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(54) MEDICINAL COMPOSITION FOR INHALATION

(57) A medicinal composition for inhalation containing a continuous-release type prodrug of an EP2 agonist topically exhibits a prolonged bronchodilating and anti-inflammatory effects. Namely, the medicinal composition for inhalation containing a continuous-release type prodrug of an EP2 agonist is useful as a safe preventive and/or a remedy for respiratory diseases (for example, asthma, pulmonary injury, pulmonary fibrosis, pulmonary

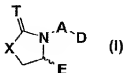
emphysema, bronchitis, chronic obstructive pulmonary disease, adult respiratory distress syndrome, cystic fibrosis, pulmonary hypertension or the like) without causing any systemic effect such as lowering blood pressure. Thus, a safe and useful remedy for respiratory diseases is provided.

EP 1 806 148 A1

Description

Technical Field

[0001] The present invention relates to a pharmaceutical composition for inhalation comprising EP2 agonist.
[0002] For more detail, it relates to a pharmaceutical composition for inhalation comprising a sustained prodrug of EP2 agonist which is long-acting and reduces hypotensive effect. Concretely, it relates to a pharmaceutical composition for inhalation comprising a compound represented by formula (I):



wherein all symbols have the same meanings as described below, a salt thereof, a solvate thereof or a cyclodextrin clathrate thereof.

Background Art

[0003] Chronic obstructive pulmonary disease (COPD) is one of the respiratory diseases and is a disease accompanying airflow obstruction in addition to chronic bronchitis, emphysema, or the complications of both diseases, and characterized by airflow limitation which is not completely reversible. Smoking or the like triggers inflammation of the bronchus or collapse of alveoli. As a result, symptoms such as cough, sputum production or shortness of breath appear, and when the disease progresses, hypoxemia will be developed. As an agent for treating COPD, a bronchodilator (for example, an anticholinergic drug, a β_2 -stimulator, a xanthine derivative or the like), an expectorant, a steroid or an antibiotic is used. With the use of a bronchodilator or an expectorant, improvement of the symptoms can be expected, however, they are not agents that fundamentally improve the pathological conditions. Additionally, long-term dosing of a steroid is not preferable in terms of side effects or the like. Accordingly, a safe and useful therapeutic agent for COPD has been demanded.

[0004] It is known that the compound described in WO03/74483 (Patent Reference 1) has EP2 agonist action and is useful for prevention and/or treatment of pulmonary injury, pulmonary fibrosis, pulmonary emphysema, bronchitis, chronic obstructive pulmonary disease etc.

[0005] However, since EP2 agonist acted on organs besides the respiratory organ, for example circulatory organs, there was fear that it lower the blood pressure of the patient having the normal blood pressure.
 [Patent Reference 1] WO2003/74483

Disclosure of the invention

Problems to be solved by the invention

[0006] An object of the present invention is to provide a safe and effective medicament which has bronchodilating and anti-inflammatory effect to treat respiratory disease.

Means for Solution of a Problem

[0007] The inventors of the present invention carried out intensive studies for the purpose of solving the above problems. As a result, they found that by administering an EP2 agonist by inhalation, a bronchodilating effect and an anti-inflammatory effect are locally exhibited and an undesired effect of the EP2 agonist, for example, an effect on circulatory organs such as a hypotensive effect can be avoided or reduced.

[0008] Additionally, the inventors of the present invention also found that as an EP2 agonist in which a desired effect in the respiratory organ can be sustained and an effect on circulatory organs can be avoided or reduced, a carboxylic acid prodrug is favorable. The inventors of the present invention particularly found that a prodrug having an ester with a high lipid-soluble long-chain aliphatic alcohol or an amide with a long-chain aliphatic amine remains in an affected area in the respiratory organ and exhibits its effect in a sustained manner for a long period of time. Namely, an inhaled prodrug of the above-mentioned EP2 agonist in an inactive form remains in an affected area, and since the ester with

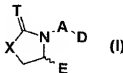
a long-chain aliphatic alcohol or the like is not susceptible to enzymatic digestion, the inactive form of EP2 agonist is gradually changed into an active form of EP2 agonist, and the desired effect is sustained in the desired organ for a long period of time. Furthermore, by inhalation of the prodrug, since the concentration of the EP2 agonist does not increase transiently, an effect on circulatory organs is avoided and a hypotensive effect can be reduced.

[0009] Additionally, with regard to an oral pharmaceutical composition, a prodrug is sometimes used for the purpose of increasing the oral absorption of an agent. However, the inventors of the present invention found an amazing effect that the effect is sustained in the respiratory organ and the hypotensive effect is reduced, which is an object completely different from that of the oral pharmaceutical composition, by using a sustained prodrug in a pharmaceutical composition for inhalation.

[0010] Therefore, they have found that EP2 agonist, particularly a pharmaceutical composition for inhalation comprising a sustained prodrug of EP2 agonist has bronchodilating and anti-inflammatory effect and it can be a safe and effective medicament, and have completed the present invention.

[0011] That is, the present invention relates to the followings.

1. A pharmaceutical composition for inhalation comprising EP2 agonist;
2. The pharmaceutical composition according to above 1, wherein the EP2 agonist is a sustained prodrug;
3. The pharmaceutical composition according to above 2, wherein the prodrug has reduced hypotensive effect;
4. The pharmaceutical composition according to above 2, wherein the prodrug is an ester of a long chain aliphatic alcohol or an amide of a long chain aliphatic amine;
5. The pharmaceutical composition according to above 1, wherein the EP2 agonist is a compound represented by formula (I):



wherein T is (1) an oxygen atom or (2) a sulfur atom,

X is (1) -CH₂-, (2) -O- or (3) -S-,

A is A¹ or A²,

A¹ is (1) C2-8 straight-chain alkylene optionally substituted by 1 to 2 C1-4 alkyl, (2) C2-8 straight-chain alkenylene optionally substituted by 1 to 2 C1-4 alkyl or (3) C2-8 straight-chain alkynylene optionally substituted by 1 to 2 C1-4 alkyl,

A² is -G¹-, G²-, G³-,

G¹ is (1) C1-4 straight-chain alkylene optionally substituted by 1 to 2 C1-4 alkyl, (2) C2-4 straight-chain alkenylene optionally substituted by 1 to 2 C1-4 alkyl or (3) C2-4 straight-chain alkynylene optionally substituted by 1 to 2 C1-4 alkyl,

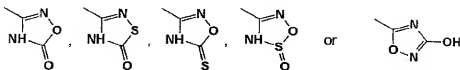
G² is (1) -Y-, (2) -ring 1-, (3) -Y-ring 1-, (4) -ring 1-Y- or (5) -Y-C1-4 alkylene-ring 1-,

Y is (1) -S-, (2) -SO-, (3) -SO₂-, (4) -O- or (5) -NR¹-,

R¹ is (1) a hydrogen atom, (2) C1-10 alkyl or (3) C2-10 acyl,

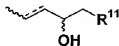
G³ is (1) a bond, (2) C1-4 straight-chain alkylene optionally substituted by 1 to 2 C1-4 alkyl, (3) C2-4 straight-chain alkenylene optionally substituted by 1 to 2 C1-4 alkyl or (4) C2-4 straight-chain alkynylene optionally substituted by 1 to 2 C1-4 alkyl,

D is (1) -COOH, (2) -COOR², (3) tetrazol-5-yl, (4) -CONR³SO₂R⁴, (5) -CH₂OH, (6) -CH₂OR⁵, (7) hydroxy, (8) -OR⁵, (9) formyl, (10) -CONR⁶R⁷, (11) -CONR⁶OR⁸, (12) -CO-(NH-amino acid residue-CO)_m-OH, (13) -O-(CO-amino acid residue-NH)_m-H, (14) -OCO-R¹⁰, (15) -COO-Z¹-Z²-Z³ or (16)



R² is hydrocarbon which may have a substituent(s),

R^3 is (1) a hydrogen atom or (2) a hydrocarbon which may have a substituent(s),
 R^4 is a hydrocarbon which may have a substituent(s),
 R^5 is a hydrocarbon which may have a substituent(s),
 R^6 and R^7 are each independently (1) a hydrogen atom or (2) a hydrocarbon which may have a substituent(s),
 R^8 and R^9 are each independently (1) a hydrogen atom or (2) a hydrocarbon which may have a substituent(s),
 R^{10} is a hydrocarbon which may have a substituent(s),
 m is 1 or 2,
 Z^1 is (1) C1-15 alkenylene, (2) C2-15 alkenylene, or (3) C2-15 alkynylene,
 Z^2 is (1) -CO-, (2) -OCO-, (3) -COO-, (4) -CONR^{Z1}-, (5) -NR^{Z2}CO-, (6) -O-, (7) -S-, (8) -SO₂-, (9) -SO₂-NR^{Z2}-,
(10) -NR^{Z2}SO₂-, (11) -NR^{Z3}-, (12) -NR^{Z4}CONR^{Z5}-, (13) -NR^{Z6}COO-, (14) -OCONR^{Z7}- or (15) -OCOO-,
 Z^3 is (1) a hydrogen atom, (2) C1-15 alkyl, (3) C2-15 alkenyl, (4) C2-15 alkynyl, (5) ring Z or (6) C1-10 alkyl substituted by C1-10 alkoxy, C1-10 alkylthio, C1-10 alkyl-NR^{Z6}- or ring Z,
ring Z is (1) a cyclic hydrocarbon, or (2) a heterocyclic ring,
 R^{Z1} , R^{Z2} , R^{Z3} , R^{Z4} , R^{Z5} , R^{Z6} , R^{Z7} and R^{Z8} are each independently a hydrogen atom or C1-15 alkyl,
 R^{Z1} and Z^3 may be taken together with the nitrogen atom to which they are attached to form a 5 to 7 membered nitrogen-containing heterocyclic ring, and the heterocyclic ring may contain other 1 to 3 hetero atom(s) selected from oxygen, nitrogen and sulfur atoms,
ring Z and 5 to 7 membered nitrogen-containing heterocyclic ring formed by R^{Z1} and Z^3 together with the nitrogen atom to which they are attached may be substituted by 1 to 3 group(s) selected from the following (1) to (4): (1) C1-15 alkyl, (2) C2-15 alkenyl, (3) C2-15 alkynyl, (4) C1-10 alkyl substituted by C1-10 alkoxy, C1-10 alkylthio or C1-10 alkyl-NR^{Z6}-,
 R^{Z9} is a hydrogen atom or C1-10 alkyl,
E is E¹ or E²,
E¹ is



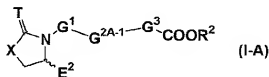
R^{11} is (1) C1-10 alkyl, (2) C1-10 alkylthio, (3) C1-10 alkyl substituted by C3-8 cycloalkyl, (4) C1-10 alkyl substituted by ring 2 or (5) C1-10 alkyl substituted by -W¹-W²-ring 2,
 W^1 is (1) -O-, (2) -S-, (3) -SO-, (4) -SO₂-, (5) -NR¹¹⁻¹-, (6) carbonyl, (7) -NR¹¹⁻¹-SO₂-, (8) carbonylamino or (9) aminocarbonyl,
 R^{11-1} is (1) a hydrogen atom, (2) C1-10 alkyl or (3) C2-10 acyl,
 W^2 is (1) a bond or (2) C1-8 alkyl optionally substituted by C1-4 alkyl, a halogen atom or hydroxy,
E² is (1) -U¹-U²-U³ or (2) ring 4,
 U^1 is (1) C1-4 alkenylene, (2) C2-4 alkenylene, (3) C2-4 alkynylene, (4) -ring 3-, (5) C1-4 alkenylene-ring 3-, (6) C2-4 alkenylene-ring 3- or (7) C2-4 alkynylene-ring 3-,
 U^2 is (1) a bond, (2) -CH₂-, (3) -CHOH-, (4) -O-, (5) -S-, (6) -SO-, (7) -SO₂-, (8) -NR¹²-, (9) carbonyl, (10) -NR¹²SO₂-, (11) carbonylamino or (12) aminocarbonyl,
 R^{12} is (1) a hydrogen atom, (2) C1-10 alkyl or (3) C2-10 acyl,
 U^3 is (1) C1-8 alkyl optionally substituted by 1 to 3 substituent(s) selected from C1-10 alkyl, halogen atom, hydroxy, C1-10 alkoxy, C1-10 alkylthio and NR¹³R¹⁴, (2) C2-8 alkenyl optionally substituted by 1 to 3 substituent(s) selected from C1-10 alkyl, a halogen atom, hydroxy, C1-10 alkoxy, C1-10 alkylthio and NR¹³R¹⁴, (3) C2-8 alkynyl optionally substituted by 1 to 3 substituent(s) selected from C1-10 alkyl, a halogen atom, hydroxy, C1-10 alkoxy, C1-10 alkylthio and NR¹³R¹⁴, (4) C1-8 alkyl substituted by ring 4 or (5) ring 4,
 R^{13} and R^{14} are each independently (1) a hydrogen atom or (2) C1-10 alkyl, ring 1, ring 2, ring 3 and ring 4 are each independently optionally substituted by 1 to 5 R,
R is (1) C1-10 alkyl, (2) C2-10 alkenyl, (3) C2-10 alkynyl, (4) C1-10 alkoxy, (5) C1-10 alkylthio, (6) halogen atom, (7) hydroxy, (8) nitro, (9) -NR¹⁵R¹⁶, (10) C1-10 alkyl substituted by C1-10 alkoxy, (11) C1-10 alkyl substituted by 1 to 3 halogen atom(s), (12) C1-10 alkyl substituted by C1-10 alkoxy substituted by 1 to 3 halogen atom(s), (13) C1-10 alkyl substituted by -NR¹⁵R¹⁶, (14) ring 5, (15) -O-ring 5, (16) C1-10 alkyl substituted by ring 5, (17) C2-10 alkenyl substituted by ring 5, (18) C2-10 alkynyl substituted by ring 5, (19) C1-10 alkoxy substituted by ring 5, (20) C1-10 alkyl substituted by -O-ring 5, (21) -COOR¹⁷, (22) C1-10 alkoxy substituted by 1 to 4 halogen atom(s), (23) formyl, (24) C1-10 alkyl substituted by hydroxy or (25) C2-10 acyl,
 R^{15} , R^{16} and R^{17} are each independently (1) hydrogen atom or (2) C1-10 alkyl, ring 5 may be substituted by 1

to 3 substituent(s) selected from the following (1) to (9): (1) C1-10 alkyl, (2) C2-10 alkenyl, (3) C2-10 alkynyl, (4) C1-10 alkoxy, (5) C1-10 alkyl substituted by C1-10 alkoxy, (6) halogen atom, (7) hydroxy, (8) C1-10 alkyl substituted by 1 to 3 halogen atom(s), (9) C1-10 alkyl substituted by C1-10 alkoxy substituted by 1 to 3 halogen atom(s);

ring 1, ring 2, ring 3, ring 4 and ring 5 are each independently (1) cyclic hydrocarbon or (2) heterocyclic ring, \equiv is a single or double bond,

\sim is α -configuration, β -configuration or a mixture thereof, a salt thereof, a solvate thereof or a cyclodextrin clathrate thereof;

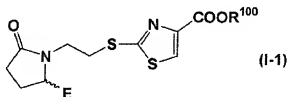
6. The pharmaceutical composition according to above 5, wherein the compound represented by formula (I) is a compound represented by formula (I-A):



wherein G^{2A-1} is -Y^a-ring-1-, Y^a is -S-, -SO₂-, -O- or -NR¹-, the other symbols have the same meanings as described in above 5;

7. The pharmaceutical composition according to above 5, wherein R² is C7-20 aliphatic hydrocarbon which may have a substituent(s);

8. The pharmaceutical composition according to above 5, wherein the compound represented by formula (I) is a compound represented by formula (I-1):



wherein R¹⁰⁰ is a hydrocarbon which may have a substituent(s), the other symbols have the same meanings as described in above 5;

9. The pharmaceutical composition according to above 8, wherein R¹⁰⁰ is an aliphatic hydrocarbon having 3 to 22 carbon atoms in its main chain which may have a substituent(s);

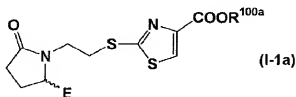
10. The pharmaceutical composition according to above 5, wherein the compound represented by formula (I) is 2-[(2-[(2R)-2-[(2-chloro-4-heptylphenoxy)methyl]-5-oxo-1-pyrrolidinyl)ethyl]sulfonyl]-1,3-thiazole-4-carboxylic acid, undecyl 2-[(2-[(2R)-2-[(3,5-dichlorophenoxy)methyl]-5-oxo-1-pyrrolidinyl)ethyl]sulfonyl]-1,3-thiazole-4-carboxylate, 10-phenyldecyl 2-[(2-[(2R)-2-[(3,5-dichlorophenoxy)methyl]-5-oxo-1-pyrrolidinyl)ethyl]sulfonyl]-1,3-thiazole-4-carboxylate, 10-phenyldecyl 2-[(2-[(5R)-2-oxo-5-[(3-(trifluoromethoxy)phenoxy)methyl]-1-pyrrolidinyl)ethyl]sulfonyl]-1,3-thiazole-4-carboxylate, undecyl 2-[(2-[(2R)-2-[(heptylamino)methyl]-5-oxo-1-pyrrolidinyl)ethyl]sulfonyl]-1,3-thiazole-4-carboxylate, 10-phenyldecyl 2-[(2-[(2R)-2-[(heptylamino)methyl]-5-oxo-1-pyrrolidinyl)ethyl]sulfonyl]-1,3-thiazole-4-carboxylate or 10-phenyldecyl 2-[(2-[(2R)-2-[(1E)-1-nonenyl]-5-oxo-1-pyrrolidinyl)ethyl]sulfonyl]-1,3-thiazole-4-carboxylate;

11. The pharmaceutical composition according to above 1, which is an agent for preventing and/or treating respiratory disease;

12. The pharmaceutical composition according to above 11, wherein the respiratory disease is asthma, pulmonary injury, pulmonary fibrosis, pulmonary emphysema, bronchitis, chronic obstructive pulmonary disease, adult respiratory distress syndrome, cystic fibrosis or pulmonary hypertension;

13. A medicament which comprises a combination of the pharmaceutical composition for inhalation comprising the compound represented by formula (I) according to above 5, a salt thereof, a solvate thereof or a cyclodextrin clathrate thereof, and one or more medicament(s) selected from type 4 phosphodiesterase inhibitor, steroids, β -agonist,

leukotriene receptor antagonist, thromboxane synthetase inhibitor, thromboxane A₂ receptor antagonist, mediator release inhibitor, anti-histamines, xanthine derivative, anticholinergic drugs, cytokine inhibitor, prostaglandins, forskolin preparation, elastase inhibitor, metalloprotease inhibitor, expectorant, antibiotics and immunosuppressive; 14. A compound represented by formula (I-1a):

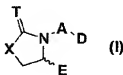


wherein R^{100a} is hydrocarbon which may have a substituent(s), with the proviso that (1) C1-10 alkyl, (2) phenyl, (3) C1-10 alkyl substituted by phenyl, (4) biphenyl, (5) C1-10 alkyl substituted by biphenyl which may be substituted by 1 to 3 substituent(s) selected from C1-10 alkyl, C1-10 alkoxy, or halogen, and (6) biphenyl which may be substituted by 1 to 3 substituent(s) selected from C1-10 alkyl, C1-10 alkoxy, or halogen are excluded, the other symbols have the same meanings as described in above 5, a salt thereof, a solvate thereof or a cyclodextrin clathrate thereof;

15. The compound according to above 14, wherein R^{100a} is C11-20 alkyl may have a substituent(s), C7-20 alkenyl may have a substituent(s) or C7-20 alkynyl may have a substituent(s), the salt thereof, the solvate thereof or the cyclodextrin clathrate thereof;

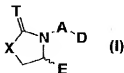
16. 2-[(2-[(2R)-2-[(2-chloro-4-heptylphenoxy)methyl]-5-oxo-1-pyrrolidinyl)ethyl)sulfanyl]-1,3-thiazole-4-carboxylic acid, undecyl 2-[(2-[(2R)-2-[(3,5-dichlorophenoxy)methyl]-5-oxo-1-pyrrolidinyl)ethyl)sulfanyl]-1,3-thiazole-4-carboxylate, 10-phenyldecyl 2-[(2-[(2R)-2-[(3,5-dichlorophenoxy)methyl]-5-oxo-1-pyrrolidinyl)ethyl)sulfanyl]-1,3-thiazole-4-carboxylate, 10-phenyldecyl 2-[(2-[(5R)-2-oxo-5-[(3-(trifluoromethoxy)phenoxy)methyl]-1-pyrrolidinyl)ethyl)sulfanyl]-1,3-thiazole-4-carboxylate, undecyl 2-[(2-[(2R)-2-[(heptylamino)methyl]-5-oxo-1-pyrrolidinyl)ethyl)sulfanyl]-1,3-thiazole-4-carboxylate, 10-phenyldecyl 2-[(2-[(2R)-2-[(heptylamino)methyl]-5-oxo-1-pyrrolidinyl)ethyl)sulfanyl]-1,3-thiazole-4-carboxylate or 10-phenyldecyl 2-[(2-[(2R)-2-[(1E)-1-nonenyl]-5-oxo-1-pyrrolidinyl)ethyl)sulfanyl]-1,3-thiazole-4-carboxylate, a salt thereof, a solvate thereof or a cyclodextrin clathrate thereof;

17. A method for preventing and/or treating respiratory disease which is characterized by inhalation administration effective dose of a compound represented by formula (I):



wherein all symbols have same meanings as described in above 5, a salt thereof, a solvate thereof or a cyclodextrin clathrate thereof;

18. A use of a pharmaceutical composition for inhalation comprising a compound represented by formula (I):



wherein all symbols have same meanings as described in above 5, a salt thereof, a solvate thereof or a cyclodextrin clathrate thereof for preparing an agent for preventing and/or treating respiratory disease.

Effect of the Invention

[0012] A pharmaceutical composition for inhalation comprising a sustained prodrug of EP2 agonist topically exhibits

a prolonged bronchodilating and antiinflammatory effects and may avoid any systemic effect such as lowering blood pressure. Therefore, the pharmaceutical composition for inhalation comprising a sustained prodrug of EP2 agonist is useful as a safe agent for preventing and/or treating respiratory diseases (for example, asthma, pulmonary injury (e.g. acute pulmonary injury, chronic pulmonary injury), pulmonary fibrosis, pulmonary emphysema, bronchitis (e.g. acute bronchitis, chronic bronchitis etc.), chronic obstructive pulmonary disease, adult respiratory distress syndrome, cystic fibrosis, pulmonary hypertension or the like).

Best mode for Carrying out the Invention

[0013] As the EP2 agonist reported previously, the compound described in EP860430, ONO-8815Ly, the compound described in JP2000-128658, the compound described in WO99/33794, the compound described in EP974580, the compound described in WO95/19964 the compound described in WO98/28264, the compound described in WO99/19300, the compound described in EP0911321, AH-13205, CP-533536, the compound described in WO98/58911, the compound described in US5,698,598, the compound described in US6,376,533, the compound described in WO2004/078103, the compound described in WO2005/012232, the compound described in WO2005/061492, the compound described in WO2005/080367, Butaprost or Rioprostil, Misoprostol and AY23626 are included. These compounds, the salts thereof, the solvates thereof or the prodrugs are preferable as a compound used in the present invention.

[0014] Moreover, the EP2 agonist includes not only a compound which has EP2 agonist activity, but also a compound which is converted into EP2 agonist by reaction with enzymes *etc.* within a living body, namely, a prodrug of EP2 agonist.

[0015] As the EP2 agonist to be used in the present invention, a compound in which the bronchodilator effect can be sustained and the hypotensive effect can be reduced is preferred. For example, the duration time of the bronchodilator effect is in the range of from 6 hours to 1 week, preferably from 6 to 48 hours, more preferably from 6 to 24 hours after administration. Furthermore, in the present invention, the reduction of hypotensive effect means that in a dose that allows a bronchodilator effect to be exhibited, a significant decrease in blood pressure is not caused and the rate of change in blood pressure is smaller than with that before administration. The significant decrease in blood pressure refers to a decrease in blood pressure by 20 to 10 mmHg from blood pressure before administration. As for a range of reduction of the hypotensive effect in the present invention, the decrease in blood pressure compared with before drug administration is preferably within 10 mmHg, and more preferably within 5 mmHg.

[0016] In the present invention, as the EP2 agonist in which the desired effect in the respiratory organs can be sustained and the hypotensive effect can be reduced, particularly a sustained prodrug of the EP2 agonist is preferred. The sustained prodrug of the EP2 agonist as used herein means a prodrug designed such that an inactive form of the EP2 agonist remains in an affected area in the respiratory organ and is gradually changed into an active form of the EP2 agonist by an enzyme *in vivo*, and the desired effect can be exhibited in the desired organ in a sustained manner for a long period of time. Since the sustained prodrug of the present invention is gradually changed into an active form of the EP2 agonist in the desired organ, the concentration of the active form of EP2 agonist in the blood does not increase transiently and the hypotensive effect is less likely to be caused.

[0017] In the present invention, a carboxylic acid prodrug is preferred as a sustained prodrug of EP2 agonist. The carboxylic acid prodrug means EP2 agonist whose the carboxy is esterified or amidated. As the sustained prodrug of EP2 agonist, an ester of a long-chain aliphatic alcohol or an amide of a long-chain aliphatic amine are preferred particularly.

[0018] In the specification, the "ester of a long-chain aliphatic alcohol" is a compound whose carboxy group is esterified with an alcohol having 3 to 22 carbon atoms in its main chain. The number of carbon atoms in the "alcohol having 3 to 22 carbon atoms in its main chain" is preferably 6 to 20, and more preferably 10 to 20. As the ester of a long-chain aliphatic alcohol, for example, decyl ester, 10-phenyldecyl ester or undecyl ester etc. is preferred. The "long-chain aliphatic alcohol" may be substituted by a substituent(s). The "substituent" has the same meaning as substituent of R² described below. Preferably, for example, phenyl or hydroxy is included.

[0019] In the specification, the "amide of a long-chain aliphatic amine" is a compound whose carboxy group is amidated with an amine substituted by aliphatic hydrocarbon having 3 to 22 carbon atoms in its main chain. The number of carbon atoms in the "amine substituted by aliphatic hydrocarbon having 3 to 22 carbon atoms in its main chain" is preferably 6 to 20, and more preferably 10 to 20. As the aliphatic hydrocarbon having 3 to 22 carbon atoms in its main chain, for example, C3-22 alkyl, C3-22 alkenyl or C3-22 alkynyl is included.

[0020] C3-22 alkyl is propyl, butyl, pentyl, hexyl, heptyl, octyl, nonyl, decyl, undecyl, dodecyl, tridecyl, tetradecyl, pentadecyl, hexadecyl, heptadecyl, octadecyl, nonadecyl, icosyl, hencicosanyl, docosanyl or isomer thereof.

[0021] C3-22 alkenyl is propenyl, butenyl, pentenyl, hexenyl, heptenyl, octenyl, nonenyl, decenyl, undecenyl, dodecenyl, tridecenyl, tetradecenyl, pentadecenyl, hexadecenyl, heptadecenyl, octadecenyl, nonadecenyl, icosenyl, hencicosenyl, docosenyl, butadienyl, pentadienyl, hexadienyl, heptadienyl, octadienyl, nonadienyl, decadienyl, undecadienyl, dodecadienyl, tridecadienyl, tetradecadienyl, pentadecadienyl, hexadecadienyl, heptadecadienyl, octadecadienyl, nonadecadienyl, icosadienyl, hencicosadienyl, docosadienyl, hexatrienyl, heptatrienyl, octatrienyl, nonatrienyl, decatrienyl, undecatrienyl, dodecatrienyl, tridecatrienyl, tetradecatrienyl, pentadecatrienyl, hexadecatrienyl, heptadecatrienyl, octa-

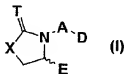
decatrienyl, nonadecatrienyl, icosatrienyl, henicosaatrienyl, docosaatrienyl or isomer thereof.

[0022] C3-22 alkynyl is propynyl, butynyl, pentynyl, hexynyl, heptynyl, octynyl, nonynyl, decynyl, undecynyl, dodecynyl, tridecynyl, tetradecynyl, pentadecynyl, hexadecynyl, heptadecynyl, octadecynyl, nonadecynyl, icosynyl, henicosaenyl, docosaenyl, butadienyl, pentadienyl, hexadienyl, heptadienyl, octadienyl, nonadienyl, decadienyl, undecadienyl, dodecadienyl, tridecadienyl, tetradecadienyl, pentadecadienyl, hexadecadienyl, heptadecadienyl, octadecadienyl, nonadecadienyl, icosadienyl, henicosaadienyl, docosaadienyl, hexatrienyl, heptatrienyl, octatrienyl, nonatrienyl, decatrienyl, undecatrienyl, dodecatrienyl, tridecatrienyl, tetradecatrienyl, pentadecatrienyl, hexadecatrienyl, heptadecatrienyl, octadecatrienyl, nonadecatrienyl, icosatrienyl, henicosaatrienyl, docosaatrienyl or isomer thereof.

[0023] Preferably the long-chain aliphatic amine is, for example, decylamine, undecylamine *etc.* The long-chain aliphatic amine may be substituted by a substituent(s). The "substituent" has the same mean as substituent of R² described below. Preferably, for example, phenyl or hydroxy is included.

[0024] As the sustained prodrg of EP2 agonist, concretely, undecyl 2-[(2-[(2R)-2-[(3,5-dichlorophenoxy)methyl]-5-oxo-1-pyrrolidinyl)ethyl)sulfanyl]-1,3-thiazole-4-carboxylate, 10-phenyldecyl 2-[(2-[(2R)-2-[(3,5-dichlorophenoxy)methyl]-5-oxo-1-pyrrolidinyl)ethyl)sulfanyl]-1,3-thiazole-4-carboxylate, 10-phenyldecyl 2-[(2-[(5R)-2-oxo-5-[(3-(trifluoromethoxy)phenoxy)methyl]-1-pyrrolidinyl)ethyl)sulfanyl]-1,3-thiazole-4-carboxylate, undecyl 2-[(2-[(2R)-2-[(heptylamino)methyl]-5-oxo-1-pyrrolidinyl)ethyl)sulfanyl]-1,3-thiazole-4-carboxylate, 10-phenyldecyl 2-[(2-[(2R)-2-[(heptylamino)methyl]-5-oxo-1-pyrrolidinyl)ethyl)sulfanyl]-1,3-thiazole-4-carboxylate or 10-phenyldecyl 2-[(2-[(2R)-2-[(1E)-1-nonenyl]-5-oxo-1-pyrrolidinyl)ethyl)sulfanyl]-1,3-thiazole-4-carboxylate, a salt thereof, a solvate thereof or a cyclodextrin clathrate thereof is preferable.

[0025] As EP2 agonist, for example, a compound represented by formula (I):



wherein all symbols have the same meanings as described above, is included.

[0026] In the specification, C1-4 alkyl is methyl, ethyl, propyl, butyl or isomer thereof.

[0027] In the specification, C1-8 alkyl is methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, octyl or isomer thereof.

[0028] In the specification, C1-10 alkyl is methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, octyl, nonyl, decyl or isomer thereof.

[0029] In the specification, C1-15 alkyl is methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, octyl, nonyl, decyl, undecyl, dodecyl, tridecyl, tetradecyl, pentadecyl or isomer thereof.

[0030] In the specification, C1-20 alkyl is methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, octyl, nonyl, decyl, undecyl, dodecyl, tridecyl, tetradecyl, pentadecyl, hexadecyl, heptadecyl, octadecyl, nonadecyl, icosyl or isomer thereof.

[0031] In the specification, C7-20 alkyl is heptyl, octyl, nonyl, decyl, undecyl, dodecyl, tridecyl, tetradecyl, pentadecyl, hexadecyl, heptadecyl, octadecyl, nonadecyl, icosyl or isomer thereof.

[0032] In the specification, C11-20 alkyl is undecyl, dodecyl, tridecyl, tetradecyl, pentadecyl, hexadecyl, heptadecyl, octadecyl, nonadecyl, icosyl or isomer thereof.

[0033] In the specification, C2-8 alkenyl is ethenyl, propenyl, butenyl, pentenyl, hexenyl, heptenyl, octenyl or isomer thereof.

[0034] In the specification, C2-10 alkenyl is ethenyl, propenyl, butenyl, pentenyl, hexenyl, heptenyl, octenyl, nonenyl, decenyl or isomer thereof.

[0035] In the specification, C2-15 alkenyl is vinyl, propenyl, butenyl, pentenyl, hexenyl, heptenyl, octenyl, nonenyl, decenyl, undecenyl, dodecenyl, tridecenyl, tetradecenyl, pentadecenyl, butadienyl, pentadienyl, hexadienyl, heptadienyl, octadienyl, nonadienyl, decadienyl, undecadienyl, dodecadienyl, tridecadienyl, tetradecadienyl, pentadecadienyl, hexadecadienyl, heptadecadienyl, octadecadienyl, nonadecadienyl, icosadienyl, henicosaadienyl, docosaadienyl, hexatrienyl, heptatrienyl, octatrienyl, nonatrienyl, decatrienyl, undecatrienyl, dodecatrienyl, tridecatrienyl, tetradecatrienyl, pentadecatrienyl or isomer thereof.

[0036] In the specification, C2-20 alkenyl is vinyl, propenyl, butenyl, pentenyl, hexenyl, heptenyl, octenyl, nonenyl, decenyl, undecenyl, dodecenyl, tridecenyl, tetradecenyl, pentadecenyl, hexadecenyl, heptadecenyl, octadecenyl, nonadecenyl, icosenyl, butadienyl, pentadienyl, hexadienyl, heptadienyl, octadienyl, nonadienyl, decadienyl, undecadienyl, dodecadienyl, tridecadienyl, tetradecadienyl, pentadecadienyl, hexadecadienyl, heptadecadienyl, octadecadienyl, nonadecadienyl, icosadienyl, henicosaadienyl, docosaadienyl, hexatrienyl, heptatrienyl, octatrienyl, nonatrienyl, decatrienyl, undecatrienyl, dodecatrienyl, tridecatrienyl, tetradecatrienyl, pentadecatrienyl, hexadecatrienyl, heptadecatrienyl, octadecatrienyl, nonadecatrienyl, icosatrienyl or isomer thereof.

[0037] In the specification, C7-20 alkenyl is heptenyl, octenyl, nonenyl, decenyl, undecenyl, dodecenyl, tridecenyl, tetradecenyl, pentadecenyl, hexadecenyl, heptadecenyl, octadecenyl, nonadecenyl, icosenyl, heptadienyl, octadienyl, nonadienyl, decadienyl, undecadienyl, dodecadienyl, tridecadienyl, tetradecadienyl, pentadecadienyl, hexadecadienyl, heptadecadienyl, octadecadienyl, nonadecadienyl, icosadienyl, heptatrienyl, octatrienyl, nonatrienyl, decatrienyl, undecatrienyl, dodecatrienyl, tridecatrienyl, tetradecatrienyl, pentadecatrienyl, hexadecatrienyl, heptadecatrienyl, octadecatrienyl, nonadecatrienyl, icosatrienyl or isomer thereof.

[0038] In the specification, C2-8 alkynyl is ethynyl, propynyl, butynyl, pentynyl, hexynyl, heptynyl, octynyl or isomer thereof.

[0039] In the specification, C2-10 alkynyl is ethynyl, propynyl, butynyl, pentynyl, hexynyl, heptynyl, octynyl, nonynyl, decynyl or isomer thereof.

[0040] In the specification, C2-15 alkynyl is ethynyl, propynyl, butynyl, pentynyl, hexynyl, heptynyl, octynyl, nonynyl, decynyl, undecynyl, dodecynyl, tridecynyl, tetradecynyl, pentadecynyl, butadiynyl, pentadiynyl, hexadiynyl, heptadiynyl, octadiynyl, nonadiynyl, decadiynyl, undecadiynyl, dodecadiynyl, tridecadiynyl, tetradecadiynyl, pentadecadiynyl, hexadecadiynyl, heptadecadiynyl, octadecadiynyl, nonadecadiynyl, icosadiynyl, heptatriynyl, octatriynyl, nonatriynyl, decatryynyl, undecatriynyl, dodecatriynyl, tridecatriynyl, tetradecatriynyl, pentadecatriynyl or isomer thereof.

[0041] In the specification, C2-20 alkynyl is ethynyl, propynyl, butynyl, pentynyl, hexynyl, heptynyl, octynyl, nonynyl, decynyl, undecynyl, dodecynyl, tridecynyl, tetradecynyl, pentadecynyl, hexadecynyl, heptadecynyl, octadecynyl, nonadecynyl, icosynyl, butadiynyl, pentadiynyl, hexadiynyl, heptadiynyl, octadiynyl, nonadiynyl, decadiynyl, undecadiynyl, dodecadiynyl, tridecadiynyl, tetradecadiynyl, pentadecadiynyl, hexadecadiynyl, heptadecadiynyl, octadecadiynyl, nonadecadiynyl, icosadiynyl, heptatriynyl, octatriynyl, nonatriynyl, decatryynyl, undecatriynyl, dodecatriynyl, tridecatriynyl, tetradecatriynyl, pentadecatriynyl, hexadecatriynyl, heptadecatriynyl, octadecatriynyl, nonadecatriynyl, icosatriynyl or isomer thereof.

[0042] In the specification, C7-20 alkenyl is heptynyl, octynyl, nonynyl, decynyl, undecynyl, dodecynyl, tridecynyl, tetradecynyl, pentadecynyl, hexadecynyl, heptadecynyl, octadecynyl, nonadecynyl, icosynyl, heptadiynyl, octadiynyl, nonadiynyl, decadiynyl, undecadiynyl, dodecadiynyl, tridecadiynyl, tetradecadiynyl, pentadecadiynyl, hexadecadiynyl, heptadecadiynyl, octadecadiynyl, nonadecadiynyl, icosadiynyl, heptatriynyl, octatriynyl, nonatriynyl, decatryynyl, undecatriynyl, dodecatriynyl, tridecatriynyl, tetradecatriynyl, pentadecatriynyl, hexadecatriynyl, heptadecatriynyl, octadecatriynyl, nonadecatriynyl, icosatriynyl or isomer thereof.

[0043] In the specification, C1-4 straight-chain alkylene is methylene, ethylene, trimethylene or tetramethylene.

[0044] In the specification, C2-8 straight-chain alkylene is ethylene, trimethylene, tetramethylene, pentamethylene, hexamethylene, heptamethylene and octamethylene.

[0045] In the specification, C1-4 alkylene is methylene, ethylene, trimethylene, tetramethylene or isomer thereof.

[0046] In the specification, C1-15 alkylene is methylene, ethylene, trimethylene, tetramethylene, pentamethylene, hexamethylene, heptamethylene, octamethylene, nonamethylene, decamethylene, undecamethylene, dodecamethylene, tridecamethylene, tetradecamethylene, pentadecamethylene or isomer thereof.

[0047] In the specification, C2-4 straight-chain alkenylene is ethylene, propylene and butylene.

[0048] In the specification, C2-8 straight-chain alkenylene, which has one or two double bond, is ethenylene, propenylene, butenylene, butadienylene, pentenylene, pentadienylene, hexenylene, hexadienylene, heptenylene, heptadienylene, octenylene and octadienylene.

[0049] In the specification, C2-4 alkenylene is ethenylene, propenylene, butenylene or isomer thereof.

[0050] In the specification, C2-15 alkenylene is ethenylene, propenylene, butenylene, pentenylene, hexenylene, heptenylene, octenylene, nonenylene, decenylene, undecenylene, dodecenylene, tridecenylene, tetradecenylene, pentadecenylene or isomer thereof.

[0051] In the specification, C2-4 straight-chain alkynylene is ethynylene, propynylene or butynylene.

[0052] In the specification, C2-8 straight-chain alkynylene, which has one or two triple bond, is ethynylene, propynylene, butynylene, butadiynylene, pentynylene, pentadiynylene, hexynylene, hexadiynylene, heptynylene, heptadiynylene, octynylene and octadiynylene.

[0053] In the specification, C2-4 alkynylene is ethynylene, propynylene, butynylene or isomer thereof.

[0054] In the specification, C2-15 alkynylene is ethynylene, propynylene, butynylene, pentynylene, hexynylene, heptynylene, octynylene, nonynylene, decynylene, undecynylene, dodecynylene, tridecynylene, tetradecynylene, pentadecynylene or isomer thereof.

[0055] In the specification, C1-10 alkoxy is methoxy, ethoxy, propoxy, butoxy, pentyloxy, hexyloxy, heptyloxy, octyloxy, nonyloxy, decyloxy or isomer thereof.

[0056] In the specification, C1-10 alkylthio is methylthio, ethylthio, propylthio, butylthio, pentylthio, hexylthio, heptylthio, octylthio, nonylthio, decylthio or isomer thereof.

[0057] In the specification, C3-8 cycloalkyl is cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl or cyclooctyl.

[0058] In the specification, C2-10 acyl is ethanoyl, propanoyl, butanoyl, pentanoyl, hexanoyl, heptanoyl, octanoyl, nonanoyl, decanoyl or isomer thereof.

[0059] In formula (I), halogen atom is fluorine, chlorine, bromine or iodine.

[0060] In the specification, amino acid of $-\text{CO}-(\text{NH-amino acid residue}-\text{CO})_m\text{OH}$ and $-\text{O}-(\text{CO-amino acid residue}-\text{NH})_m\text{H}$, which means natural amino acid or abnormal amino acid, includes, for example, glycine, alanine, valine, leucine, isoleucine, serine, threonine, cysteine, methionine, proline, asparagine, glutamine, phenylalanine, tyrosine, tryptophan, aspartic acid, glutamic acid, lysine, arginine, histidine, β -alanine, cystathionine, cystine, homoserine, isoleucine, lanthionine, norleucine, norvaline, ornithine, sarcosine, thyronine etc.

[0061] In amino acid residue in $-\text{CO}-(\text{NH-amino acid residue}-\text{CO})_m\text{OH}$ and $-\text{O}-(\text{CO-amino acid residue}-\text{NH})_m\text{H}$, an amino acid with protecting group is included.

[0062] In the specification, the "cyclic hydrocarbon" represented by ring 1, ring 2, ring 3, ring 4, ring 5 or ring Z is included an "unsaturated cyclic hydrocarbon" or a "saturated cyclic hydrocarbon". The "saturated cyclic hydrocarbon" is a "3-15 membered saturated cyclic hydrocarbon" which is cycloalkane such as cyclopropane, cyclobutane, cyclopentane, cyclohexane, cycloheptane, cyclooctane, cyclononane, cyclodecane, cycloundecane, cyclododecane, cyclotridecane, cyclotetradecane or cyclopentadecane, perhydropentalene, perhydroazulene, perhydroindene, perhydronaphthalene, perhydroheptalene, spiro[4.4]nonane, spiro[4.5]decane, spiro[5.5]undecane, bicyclo[2.2.1]heptane, bicyclo[3.1.1]heptane, bicyclo[2.2.2]octane, adamantane or noradamantane etc. The "unsaturated cyclic hydrocarbon" is included a "3-15 membered unsaturated cyclic hydrocarbon" which is cycloalkene such as cyclopentene, cyclohexene, cycloheptene, cyclooctene, cyclopentadiene, cyclohexadiene, cycloheptadiene or cyclooctadiene, aromatic hydrocarbon such as benzene, azulene, naphthalene, phenanthrene, anthracene or biphenyl (for example, 2-phenylphenyl, 3-phenylphenyl and 4-phenylphenyl etc.), pentalene, inden, indan, dihydronaphthalene, tetrahydronaphthalene, heptalene, biphenylene, as-indacene, s-indacene, acenaphthene, acenaphthylene, fluorene, phenalene, bicyclo[2.2.1]hept-2-ene, bicyclo[3.1.1]hept-2-ene or bicyclo[2.2.2]oct-2-ene etc.

[0063] In the specification, the "heterocyclic ring" represented by ring 1, ring 2, ring 3, ring 4, ring 5 or ring Z is mono-, bi- or tri-heterocyclic ring which may have 1 to 7 hetero atom(s) selected from nitrogen atom, oxygen atom and sulfur atom. The "heterocyclic ring" includes, for example, a "3 to 15 membered mono-, bi- or tri-unsaturated heterocyclic ring" or a "3 to 15 membered mono-, bi- or tri-saturated heterocyclic ring" etc.

[0064] The "3 to 15 membered mono-, bi- or tri-unsaturated heterocyclic ring" includes, for example, mono-aromatic heterocyclic ring such as pyrrole, imidazole, triazole, tetrazole, pyrazole, pyridine, pyrazine, pyrimidine, pyridazine, triazine, furan, thiophene, oxazole, isoxazole, thiazole, isothiazole, furazan, oxadiazole or thiadiazole, condensed aromatic heterocyclic ring such as indole, isindole, benzofuran, isobenzofuran, benzothiophene, isobenzothiophene, indazole, quinoline, isquinoline, purine, phthalazine, pteridine, naphthyridine, quinoxaline, quinoxaline, cinnoline, benzoxazole, benzothiazole, benzimidazole, benzofurazan, benzothiadiazole, benzotriazole, carbazole, β -carboline, acridine, phenazine, dibenzofuran, dibenzothiophene, phenanthridine, phenanthroline or perimidine, fused non-aromatic heterocyclic ring such as azepine, diazepine, pyran, oxepine, thiofuran, thiapine, oxazine, oxadiazole, oxazepine, oxadiazepine, thiazine, thiadiazine, thiazepine, thiadiazepine, indolizine, dithianaphthalene, quinoline, chromene, bert-zoxepine, benzoxazepine, benzoxadiazepine, benzothiepine, benzothiazepine, benzothiadiazepine, benzazepine, benzodiazepine, xanthen, phenothiazine, phenoxazine, phenoxathin, thianthrene, pyrrolone, imidazoline, triazoline, tetrazoline, pyrazoline, dihydropyridine, tetrahydropyridine, dihydropyrazine, tetrahydropyrazine, dihydropyrimidine, tetrahydropyrimidine, dihydropyridazine, tetrahydropyridazine, tetrahydrotriazine, dihydroazepine, tetrahydroazepine, dihydrodiazepine, tetrahydrodiazepine, dihydrofuran, dihydropyran, dihydrooxepine, tetrahydrooxepine, dihydrothiepine, dihydrothiepine, tetrahydrothiepine, dihydrooxazole, dihydroisoxazole, dihydrothiazole, dihydroisothiazole, dihydrofurazan, dihydrooxadiazole, dihydrooxazine, dihydrooxadiazine, dihydrooxazepine, tetrahydrooxazepine, dihydrooxadiazepine, tetrahydrooxadiazepine, dihydrothiadiazole, dihydrothiazine, dihydrothiadiazine, dihydrothiazepine, tetrahydrothiazepine, dihydrothiadiazepine, dihydrothiadiazepine, tetrahydrothiadiazepine, indoline, isindoline, dihydrobenzofuran, dihydroisobenzofuran, dihydrobenzothiophene, dihydroisobenzothiophene, dihydroindazole, dihydroquinoline, tetrahydroquinoline, dihydroisquinoline, tetrahydroisquinoline, tetrahydrophthalazine, tetrahydrophthalazine, dihydronaphthyridine, tetrahydronaphthyridine, dihydroquinoxaline, tetrahydroquinoxaline, dihydroquinoxaline, tetrahydroquinoxaline, dihydrocinoline, tetrahydrocinoline, benzoxathiane, dihydrobenzoxazine, dihydrobenzothiazine, pyrazinomorphone, dihydrobenzoxazole, dihydrobenzothiazole, dihydrobenzimidazole, dihydrobenzazepine, tetrahydrobenzazepine, dihydrobenzodiazepine, tetrahydrobenzodiazepine, benzodioxepane, dihydrobenzoxazepine, tetrahydrobenzoxazepine, dihydrocarbazole, tetrahydrocarbazole, dihydro- β -carboline, tetrahydro- β -carboline, dihydroacridine, tetrahydroacridine, dihydrodibenzofuran, dihydrodibenzothiophene, tetrahydrodibenzofuran, tetrahydrodibenzothiophene, dioxaindan, benzodioxane, chroman, benzodithiolane, benzodithiane, 6,7,8,9-tetrahydro-5H-pyrido[4',3':4'']pyrrolo[2,3-b]pyridine, 2,3,4,5-tetrahydro-1H-pyrido[4,3-b]indole or 6,7,8,9-tetrahydro-5H-pyrido[3',4':4'']pyrrolo[2,3-b]pyridine etc. The "3 to 15 membered mono-, bi- or tri-saturated heterocyclic ring" includes, for example, aziridine, azetidine, pyrrolidine, imidazolidine, triazolidine, tetrazolidine, pyrazolidine, piperidine, piperazine, perhydropyrimidine, perhydropyridazine, perhydroazepine, perhydrodiazepine, perhydroazocine, oxirane, oxetane, tetrahydrofuran, tetrahydropyran, perhydrooxepine, thirane, thietane, tetrahydrothiepine, tetrahydrothiopyran, perhydrothiepine, tetrahydrooxazole (oxazolidine), tetrahydroisoxazole (isoxazolidine), tetrahydrothiazole (thiazolidine), tetrahydroisothiazole (isothiazolidine), tetrahydro-

furazan, tetrahydrooxadiazole (oxadiazolidine), tetrahydrooxazine, tetrahydrooxadiazine, perhydrooxazepine, perhydrooxadiazepine, tetrahydrothiadiazole (thiadiazolidine), tetrahydrothiazine, tetrahydrothiadiazine, perhydrothiazepine, perhydrothiadiazepine, morpholine, thiomorpholine, oxathiane, perhydrobenzofuran, perhydroisobenzofuran, perhydrobenzothiophene, perhydroisobenzothiophene, perhydroindazole, perhydroquinoline, perhydroisocoumarin, perhydrophthalazine, perhydrodiphenylhydrazine, perhydroquinoxaline, perhydroquinazoline, perhydrocinnoline, perhydrobenzoxazole, perhydrobenzothiazole, perhydrobenzimidazole, perhydrocarbazole, perhydro- β -carbolone, perhydroacridine, perhydrobenzofuran, perhydrobenzothiothiophene, dioxolane, dioxane, dithiolane, dithiane *etc.*

[0065] In the specification, the "5 to 7 membered nitrogen-containing heterocyclic ring" is 5 to 7 membered heterocyclic ring which contains at least one nitrogen atom in addition to carbon atom and may be contain 1 to 3 hetero atom(s) selected from oxygen atom, nitrogen atom and sulfur atom. For example, a "5 to 7 membered nitrogen-containing unsaturated heterocyclic ring" or a "5 to 7 membered nitrogen-containing saturated heterocyclic ring" is included. Concretely, the "5 to 7 membered nitrogen-containing unsaturated heterocyclic ring" includes, for example, pyrrole, imidazole, triazole, tetrazole, pyrazole, pyrroline, azepine, imidazoline, triazoline, tetrazoline, pyrazoline, dihydropyridine, tetrahydropyridine, dihydropyrazine, tetrahydropyrazine, dihydropyrimidine, tetrahydropyrimidine, dihydropyridazine, tetrahydropyridazine, dihydroazepine, dihydroazepine, dihydrodiazepine, tetrahydrodiazepine, dihydrooxazole, dihydroisoxazole, dihydrothiazole, dihydroisothiazole, dihydrofurazan, dihydrooxadiazole, dihydrooxazine, dihydrooxadiazine, dihydrooxazepine, tetrahydrooxazepine, dihydrooxadiazepine, tetrahydrooxadiazepine, dihydrothiazole, dihydrothiazepine, dihydrothiadiazepine, tetrahydrothiazepine, dihydrothiadiazepine, tetrahydrothiadiazepine *etc.* The 5-7 membered nitrogen-containing saturated heterocyclic ring" includes pyrrolidine, imidazolidine, triazolidine, tetrazolidine, pyrazolidine, piperidine, piperazine, perhydropyrimidine, perhydropyridazine, perhydroazepine, perhydrodiazepine, tetrahydrooxazole (oxazolidine), tetrahydroisoxazole (isoxazolidine), tetrahydrothiazole (thiazolidine), tetrahydroisothiazole (isothiazolidine), tetrahydrofurazan, tetrahydrooxadiazole (oxadiazolidine), tetrahydrooxazine, tetrahydrooxadiazine, perhydrooxazepine, perhydrooxadiazepine, tetrahydrothiadiazole (thiadiazolidine), tetrahydrothiazine, tetrahydrothiadiazine, perhydrothiazepine, perhydrothiadiazepine, morpholine, thiomorpholine *etc.*

[0066] The "hydrocarbon" in "hydrocarbon which may have a substituent(s)" represented by R² included, for example, straight or branched chain aliphatic hydrocarbon or cyclic hydrocarbon *etc.*

[0067] The "straight or branched chain aliphatic hydrocarbon" is included, for example, a "C1-20 aliphatic hydrocarbon". The "C1-20 aliphatic hydrocarbon" is included, for example, C1-20 alkyl, C2-20 alkenyl, C2-20 alkynyl *etc.* The "C1-20 alkyl", the "C2-20 alkenyl" and the "C2-20 alkynyl" have the same meanings as defined above.

[0068] The "cyclic hydrocarbon" has the same meaning as the "cyclic hydrocarbon" in ring 1, ring 2, ring 3, ring 4, ring 5 or ring Z.

[0069] Preferably, the "hydrocarbon" in the "hydrocarbon which may have a substituent(s)" represented by R² is C7-20 aliphatic hydrocarbon.

[0070] The "substituent" in the "hydrocarbon which may have a substituent(s)" represented by R² includes (1) hydrocarbon which may have a substituent(s) such as C1-10 alkyl, phenyl, amino, C1-10 alkoxy, sulfo, halogen atom, carboxy, cyano, nitro, oxo, thioxo, hydroxy, trifluoromethyl or trifluoromethoxy. As used herein, the "hydrocarbon" has the same meaning as above-described "hydrocarbon". (2) heterocyclic ring may have a substituent(s) such as hydrocarbon (the "hydrocarbon" has the same meaning as above-described "hydrocarbon"), amino, sulfo, halogen atom, carboxy, cyano, nitro, oxo, thioxo, hydroxy, methoxy, trifluoromethyl, trifluoromethoxy or acetyl. As used herein, the "heterocyclic ring" has the same meaning as the "heterocyclic ring" in ring 1, ring 2, ring 3, ring 4, ring 5 or ring Z. (3) amino, (4) C1-6 acylamino such as acetylamino or propionylamino, (5) primary or secondary amino substituted by hydrocarbon (for example, methylamino, ethylamino, propylamino, isopropylamino, butylamino, heptylamino, octylamino, dimethylamino, diethylamino, cyclohexylamino, 1-carbamoyl-2-cyclohexylethylamino, N-butyl-N-cyclohexylmethylamino, phenylamino, 6,6-dimethylbicyclo[3.1.1]heptylmethylamino *etc.*). As used herein, the "hydrocarbon" has the same meaning as above-described "hydrocarbon" and is optionally substituted halogen atom, oxo, amino, carbamoyl *etc.* (6) C1-4 alkylsulfonylamino such as methylsulfonylamino or ethylsulfonylamino, (7) phenylsulfonylamino, (8) C1-4 alkylsulfonyl such as methylsulfonyl or ethylsulfonyl, (9) phenylsulfonyl, (10) halogen atom such as fluorine, chlorine, bromine or iodine, (11) carboxy, (12) cyano, (13) nitro, (14) oxo, (15) thioxo, (16) hydroxy, (17) C1-10 alkoxy such as methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, sec-butoxy, tert-butoxy, cyclohexylmethoxy or benzyloxy, (18) C3-8 cycloalkoxy such as cyclohexyloxy, (19) phenoxymethyl or phenoxymethyl, (20) phenoxymethyl, (21) mercapto, (22) C1-4 alkylthio such as methylthio, ethylthio, propylthio, isopropylthio, butylthio or tert-butylthio, (23) phenylthio, (24) carbamoyl, (25) aminocarbonyl which may be substituted by C1-8 hydrocarbon (for example, N-butylaminocarbonyl, N-cyclohexylmethylaminocarbonyl, N-butyl-N-cyclohexylmethylaminocarbonyl, N-cyclohexylaminocarbonyl, phenylaminocarbonyl *etc.*). As used herein, the "hydrocarbon" has the same meaning as the above-described "hydrocarbon". (26) sulfamoyl, (27) aminosulfonyl substituted by hydrocarbon (for example, methylaminosulfonyl *etc.*). As used herein, the "hydrocarbon" has the same meaning as above-described "hydrocarbon". (28) aminosulfonyl substituted by hydrocarbon substituted by amino (for example, dimethylaminoethylaminosulfonyl, dimethylaminopropylaminosulfonyl *etc.*). As used herein, the "hydrocarbon" has the same meaning as

above-described "hydrocarbon". (29) C1-6 alkoxy carbonyl such as methoxycarbonyl, ethoxycarbonyl, tert-butoxycarbonyl, (30) sulfo ($-\text{SO}_3\text{H}$), (31) sulfino, (32) phosphono, (33) amidino, (34) imino, (35) $-\text{B}(\text{OH})_2$, (36) C1-4 alkylsulfanyl such as methylsulfanyl or ethylsulfanyl, (37) C1-6 acyl such as formyl, acetyl, propionyl or butyl, (38) benzoyl, (39) hydroxyimino, (40) C1-8 alkoxyimino such as methoxyimino or ethoxyimino etc. The "hydrocarbon which may have a substituent(s)" may have 1 to 5 substituent(s) selected from above (1) to (49). When the number of substituent is two or more, the substituents are the same or different.

[0071] Preferably, the "substituent" in the "hydrocarbon which may have a substituent(s)" represented by R^2 is, for example, phenyl or hydroxy etc.

[0072] The "substituent" in the "hydrocarbon which may have a substituent(s)" represented by R^3 , R^4 , R^5 , R^6 , R^7 , R^8 , R^9 or R^{10} has the same meaning as the "substituent" in the "hydrocarbon which may have a substituent(s)" in R^2 .

[0073] Preferably, A is A^1 or A^2 in formula (I), more preferably A^2 .

[0074] Preferably, ring 1 is C3-10 cyclic hydrocarbon or 3 to 10 membered heterocyclic ring, more preferably C3-7 cyclic hydrocarbon or 3 to 7 membered heterocyclic ring.

[0075] More preferably, ring 1 is C5 or 6 cyclic hydrocarbon or 5 or 6 membered heterocyclic ring, especially furan, thiophene, oxazole or benzene.

[0076] Preferably, D is $-\text{COOH}$, $-\text{COOR}^2$ or $-\text{COO}-\text{Z}^1-\text{Z}^2$.

[0077] Preferably, R^2 is C7-20 aliphatic hydrocarbon which may have a substituent(s).

[0078] Preferably, Z^1 is C1-15 alkylene, more preferably C1-8 alkylene, especially C1-4 alkylene.

[0079] Preferably, Z^2 is $-\text{CO}-$, $-\text{OCO}-$, $-\text{COO}-$, $-\text{CONRZ}^1$, $-\text{OCONRZ}^1$, $-\text{OCOO}-$, more preferably $-\text{OCO}-$, $-\text{OCONRZ}^1$, $-\text{OCOO}-$.

[0080] Preferably, Z^3 is C1-15 alkyl, C1-10 alkoxy, C1-10 alkylthio, C1-10 alkyl-NR 2 , or C1-10 alkyl substituted by ring Z, more preferably C4-12 alkyl.

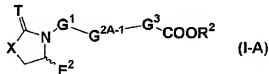
[0081] Preferably, T is oxygen atom or sulfur atom in formula (I), more preferably oxygen.

[0082] Preferably, X is $-\text{CH}_2-$, $-\text{O}-$ or $-\text{S}-$ in formula (I), more preferably $-\text{CH}_2-$.

[0083] Preferably, E is E^2 in formula (I).

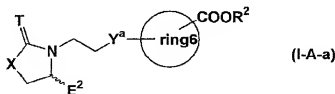
[0084] Preferably, E^2 is $-\text{U}^1-\text{U}^2-\text{U}^3$. Preferably, U^1 is C1-4 alkylene, C2-4 alkenylene or C2-4 alkynylene. Preferably, U^2 is $-\text{CHOH}-$, $-\text{O}-$, $-\text{S}-$, $-\text{SO}-$, $-\text{SO}_2-$ or $-\text{NR}^{12}-$.

[0085] Preferably, the compound represented by formula (I) is the compound represented by formula (I-A):



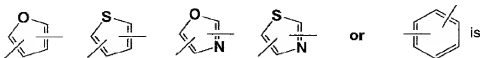
wherein G^{2A-1} is $-\text{Y}^a$ -ring 1-, Y^a is $-\text{S}-$, $-\text{SO}_2-$, $-\text{O}-$ or $-\text{NR}^1-$, the other symbols have the same meanings as described above.

[0086] Preferably, the compound represented by formula (I-A) is the compound represented by formula (I-A-a):



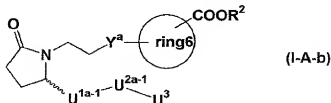
wherein ring 6 is C5 or 6 cyclic hydrocarbon or 5 or 6 membered heterocyclic ring, R^2 is hydrocarbon which may have a substituent(s), the other symbols have the same meanings as described above.

[0087] Preferably, ring 6 is furan, thiophene, oxazole, thiazole or benzene. That is,



included. Binding site can be anywhere other than same carbon.

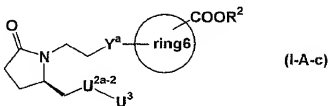
[0088] More preferably, the compound represented formula (I-A) is the compound represented by formula (I-A-b):



wherein U^{1a-1} is C1-4 alkylene, C2-4 alkenylene, C2-4 alkynylene,

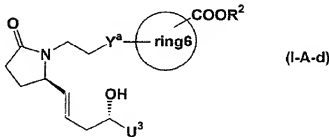
U^{2a-1} or -CHOH-, -O-, -S-, -SO-, -SO₂-, -NR¹²-,

15 the other symbols have the same meanings as described above, the compound represented by formula (I-A-c):



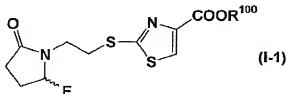
wherein U^{2a-2} is -O- or -NR¹²-,

the other symbols have the same meanings as described above, or the compound represented by formula (I-A-d):



wherein all symbols have the same meanings as described above.

[0089] Preferably, the compound represented by formula (I) is, for example, the compound represented by



wherein R¹⁰⁰ is hydrocarbon which may have a substituent(s),

55 the other symbol have the same meanings as described above. The hydrocarbon in the "hydrocarbon which may have a substituent(s)" represented by R¹⁰⁰ has the same meaning as the "hydrocarbon which may have a substituent(s)" represented by R². Preferably, R¹⁰⁰ is hydrocarbon which has 3 to 22 carbon atoms in its main chain and may have a substituent(s), more preferably hydrocarbon which has 6 to 20 carbon atoms in its main chain and may have a substituent

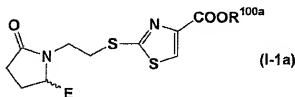
(s). Especially, hydrocarbon which has 10 to 20 carbon atoms in its main chain and may have a substituent(s) is preferred. As used herein, the substituent in the "hydrocarbon which may have a substituent(s)" represented by R^{100} has the same meaning as the "hydrocarbon which may have a substituent(s)" represented by R^2 . Preferably, for example, phenyl or hydroxy etc. is included.

[0090] Preferably, the compound used as the pharmaceutical composition for inhalation in the present invention is 2-[(2-[(2R)-2-[(2-chloro-4-heptylphenoxy)methyl]-5-oxo-1-pyrrolidinyl)ethyl)sulfanyl]-1,3-thiazole-4-carboxylic acid, undecyl 2-[(2-[(2R)-2-[(3,5-dichlorophenoxy)methyl]-5-oxo-1-pyrrolidinyl)ethyl)sulfanyl]-1,3-thiazole-4-carboxylate, 10-phenyldecyl 2-[(2-[(2R)-2-[(3,5-dichlorophenoxy)methyl]-5-oxo-1-pyrrolidinyl)ethyl)sulfanyl]-1,3-thiazole-4-carboxylate, 10-phenyldecyl 2-[(2-[(5R)-2-oxo-5-[(3-(trifluoromethoxy)phenoxy)methyl]-1-pyrrolidinyl)ethyl)sulfanyl]-1,3-thiazole-4-carboxylate, undecyl 2-[(2-[(2R)-2-[(heptylamino)methyl]-5-oxo-1-pyrrolidinyl)ethyl)sulfanyl]-1,3-thiazole-4-carboxylate, 10-phenyldecyl 2-[(2-[(2R)-2-[(heptylamino)methyl]-5-oxo-1-pyrrolidinyl)ethyl)sulfanyl]-1,3-thiazole-4-carboxylate or 10-phenyldecyl 2-[(2-[(2R)-2-[(1E)-1-nonenyl]-5-oxo-1-pyrrolidinyl)ethyl)sulfanyl]-1,3-thiazole-4-carboxylate etc.

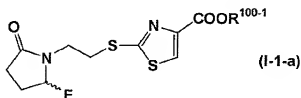
[0091] Preferred compounds are all described in Example.

[0092] Moreover, for example, 2-[(2-[(2R)-2-[(1E,4S)-4-(1-ethylcyclobutyl)-4-hydroxybut-1-enyl]-5-oxopyrrolidin-1-yl)ethyl)sulfanyl]-1,3-thiazole-4-carboxylic acid, 2-[(2-[(2R)-2-[(3,5-dichlorophenoxy)methyl]-5-oxopyrrolidin-1-yl)ethyl)thio]-1,3-thiazole-4-carboxylic acid, 2-[(2-[(2R)-2-[(2-chloro-3-(trifluoromethyl)phenoxy)methyl]-5-oxopyrrolidin-1-yl)ethyl)sulfanyl]-1,3-thiazole-4-carboxylic acid, 2-[(2-[(5R)-2-oxo-5-[(3-(trifluoromethoxy)phenoxy)methyl]pyrrolidin-1-yl)ethyl)sulfanyl]-1,3-thiazole-4-carboxylic acid or butyl 2-[(2-[(2R)-2-[(3,5-dichlorophenoxy)methyl]-5-oxopyrrolidin-1-yl)ethyl)thio]-1,3-thiazole-4-carboxylate etc. is preferred.

[0093] Meanwhile, the compound represented by formula (I-1a):



wherein R^{100a} is hydrocarbon which may have a substituent(s), with the proviso that, (1) C1-10 alkyl, (2) phenyl, (3) C1-10 alkyl substituted by phenyl, (4) biphenyl, (5) C1-10 alkyl substituted by biphenyl which may have 1 to 3 substituent(s) selected from C1-10 alkyl, C1-10 alkoxy or halogen atom and (6) biphenyl substituted by 1 to 3 substituent(s) selected from C1-10 alkyl, C1-10 alkoxy or halogen atom are excluded, the other symbol has the same meaning as described above, is a new compound among the compound represented by formula (I-1) in the present invention. Especially preferred is the compound represented by formula (I-1-a):



wherein R^{100-1} is C11-20 alkyl which may have a substituent(s), C7-20 alkenyl which may have a substituent(s) or C7-20 alkynyl which may have a substituent(s), the other symbol has the same meanings as described above. The substituent in the "C11-20 alkyl which may have a substituent(s)", "C7-20 alkenyl which may have a substituent(s)" and "C7-20 alkynyl which may have a substituent(s)" represented by R^{100-1} has the same meaning as the substituent in the "hydrocarbon which may have a substituent(s)" represented by above-described R^2 . For example, phenyl or hydroxy is preferred.

[0094] According to the present invention, unless otherwise indicated and as is apparent for those skilled in the art,

the symbol indicates that it is bound to the opposite side of the sheet (namely α -configuration), the symbol indicates that it is bound to the front side of the sheet (namely β -configuration), the symbol indicates that it is a

α -configuration, β -configuration or a mixture thereof which may be mixed by voluntary ratio, and the symbol indicates that it is a mixture of α -configuration and β -configuration which may be mixed by voluntary ratio.

[0095] Unless otherwise specified, all isomers are included in the present invention. For example, alkyl, alkenyl, alkynyl, alkoxy, alkylthio, alkylene, alkenylene or alkynylene includes straight-chain or branched-chain ones. In addition, isomers on double bond, ring, fused ring (E-, Z-, cis-, trans-isomer), isomers generated from asymmetric carbon atom(s) (R-, S-isomer, α -, β -configuration, enantiomer, diastereomer), optically active isomers (D-, L-, d-, l-isomer), polar compounds generated by chromatographic separation (more polar compound, less polar compound), equilibrium compounds, rotational isomers, mixtures thereof at voluntary ratios and racemic mixtures are also included in the present invention.

[0096] The salt of the compound represented by formula (I) includes pharmacologically acceptable salts *etc.* Preferably the pharmacologically acceptable salt is a low-toxic and water-soluble one. The suitable salt includes, for example, salts of alkali metals (e.g., potassium, sodium, lithium, *etc.*), salts of alkaline earth metals (e.g., calcium, magnesium, *etc.*), ammonium salts (e.g., tetramethylammonium salt, tetrabutylammonium salt, *etc.*), salts of organic amine (e.g., triethylamine, methylamine, dimethylamine, cyclopentylamine, benzylamine, phenethylamine, piperidine, monoethanolamine, diethanolamine, tris(hydroxymethyl)methylamine, lysine, arginine, N-methyl-D-glucamine, *etc.*), acid addition salts [salts of inorganic acids (e.g., hydrochloride, hydrobromide, hydroiodide, sulfate, phosphate, nitrate *etc.*), and salts of organic acids (e.g., acetate, trifluoroacetate, lactate, tartrate, oxalate, fumarate, maleate, benzoate, citrate, methanesulfonate, ethanesulfonate, benzenesulfonate, toluenesulfonate, isethionate, glucuronate, gluconate *etc.*)].

[0097] Moreover, the salt includes a quaternary ammonium salt. The quaternary ammonium salt is the compound represented by formula (I) wherein the nitrogen atom is quaternized by R^Q which is C1-8 alkyl or C1-8 alkyl substituted by phenyl. In the present invention, an N-oxide of the compound represented by formula (I) is included. The N-oxide is the compound wherein nitrogen is oxidized. Moreover the N-oxide may be converted into an alkaline (earth) metal, an ammonium salt, an organic amine salt or an acid addition salt.

[0098] As the suitable solvate of the compound represented formula (I), for example, water or alcohol solvents such as ethanol are included. The non-toxic and water-soluble solvate is preferred. Moreover, the solvate of the present invention includes a solvate of an alkaline (earth) metal, an ammonium salt, an organic amine salt, an acid addition salt or an N-oxide of the compound represented by formula (I) described above.

[0099] The compound of the present invention may be converted into the salt, the N-oxide or the solvate described above by the known method.

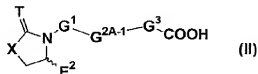
[0100] The compounds of represented by formula (I) may be converted into the corresponding cyclodextrin clathrates by the method described in the specification of JP-B-50-3362, 52-31404 or 61-52146 using α -, β - or γ -cyclodextrin or a mixture thereof. Converting into the corresponding cyclodextrin clathrates serves to increase the stability and solubility in water of the compounds, and therefore it is useful in the use for pharmaceuticals.

Processes for the preparation of the compound in the present invention

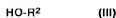
[0101] EP2 agonist used in the present invention can be prepared by the methods by methods which properly improved and combined the methods described in EP860430, JP2000-128858, WO99/33794, EP974580, WO95/19964, WO98/28264, WO99/19300, EP0911321, WO98/58911, US5,698,598, US6,376,533, WO2005/061492 or WO2005/080367, the methods based on them or the methods described in Example of the present invention.

[0102] The compound represented by formula (I) of the present invention can be prepared by the methods which properly improved and combined known the methods such as the methods described in Comprehensive Organic Transformations : A Guide to Functional Group Preparations, 2nd Edition (Richard C. Larock, John Wiley & Sons Inc, 1999) or WO2003/74483, the methods based on them or the methods described in Example of the present invention.

[0103] The compound represented by formula (I-A) can be prepared by esterifying the carboxylic acid derivative of formula (II):



wherein all symbols have the same meanings as described above, and alcohol represented by



wherein R² has the same meaning as described above, as follows.

[0104] The esterification is known. For example, it includes (1) dehydration-condensation reaction in the presence of acid catalyst, (2) ester exchange reaction, etc.

(1) dehydration-condensation reaction in the presence of acid catalyst

The compound represented by formula (I) can be prepared, for example, by reaction of the carboxylic acid derivative represented by formula (II) in an organic solvent which is alcohol represented by formula (III) or a mixed solvent of the alcohol and the other organic solvent, in the presence of acid such as an inorganic acid (e.g. sulfuric acid, hydrochloric acid), an organic acid (e.g. p-toluene sulfonic acid, trifluoroacetic acid) or Lewis acid (e.g. trifluoroborane-diethyl ether complex) at 0 to 100 °C.

(2) ester exchange reaction

The compound represented by formula (I) can be prepared, for example, by reaction of the simple ester such as methyl ester of the carboxylic acid derivative represented by formula (II) in alcohol solvent represented by formula (III), in the presence of acid such as an inorganic acid (e.g. sulfuric acid, hydrochloric acid), an organic acid (e.g. p-toluene sulfonic acid, trifluoroacetic acid) or Lewis acid (e.g. trifluoroborane-diethyl ether complex), a base such as potassium carbonate, sodium carbonate, cesium carbonate, t-butoxy potassium, sodium methoxide, sodium ethoxide, or titanium alkoxide such as titanium tetraisopropoxide at 0 to 100 °C.

In addition to the above esterification, the following esterifications such as (3) the method using an acyl halide, (4) the method using a mixed acid anhydride and (5) the method using a condensing agent may be used.

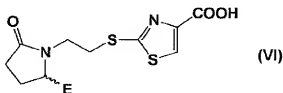
These methods are explained concretely below.

(3) The method using an acyl halide may be carried out, for example, by reacting carboxylic acid with an acyl halide (e.g. oxalyl chloride or thionyl chloride etc.) in an organic solvent (e.g. chloroform, dichloromethane, diethyl ether or tetrahydrofuran) or without a solvent at -20 °C to reflux temperature, and then the obtained acyl halide derivative may be reacted with alcohol in an organic solvent (e.g. chloroform, dichloromethane, diethyl ether or tetrahydrofuran) in the presence of a base (e.g. pyridine, triethylamine, dimethylaniline, dimethylaminopyridine or diisopropylethylamine etc.) at 0 to 40 °C. As an alternative, the obtained acyl halide derivative may be reacted in an organic solvent (e.g. dioxane, tetrahydrofuran) using an alkaline aqueous solution (e.g. sodium bicarbonate, sodium hydroxide) at 0 to 40 °C.

(4) The method using a mixed acid anhydride may be carried out, for example, by reacting carboxylic acid with an acyl halide (e.g. pivaloyl chloride, tosyl chloride or mesyl chloride) or an acid derivative (e.g. ethyl chloroformate or isobutyl chloroformate) in an organic solvent (e.g. chloroform, dichloromethane, diethyl ether, tetrahydrofuran) or without a solvent, in the presence of a base (e.g. pyridine, triethylamine, dimethylaniline, dimethylaminopyridine or diisopropylethylamine) at 0 to 40 °C, and then the obtained mixed acid anhydride derivative may be reacted with alcohol in an organic solvent (e.g. chloroform, dichloromethane, diethyl ether or tetrahydrofuran), at 0 to 40 °C.

(5) The method using a condensing agent may be carried out, for example, by reacting carboxylic acid with alcohol in an organic solvent (e.g. chloroform, dichloromethane, dimethylformamide, diethyl ether or tetrahydrofuran) or without a solvent, in the presence or absence of a base (e.g. pyridine, triethylamine, dimethylaniline or dimethylaminopyridine), using a condensing agent (e.g. 1, 3-dicyclohexyl carbodiimide (DCC), 1-ethyl-3-[3-(dimethylamino)propyl] carbodiimide (EDC), 1, 1'-carbodiimidazole (CDI), 2-chloro-1-methylpyridinium iodide, or 1-propanephosphonic acid cyclic anhydride (PPA)), in the presence or absence of 1-hydroxybenzotriazole (HOBt) at 0 to 40 °C.

[0105] The compound represented by formula (1-1) can be prepared by the above esterification of the compound represented by formula (VI):



wherein all symbols have the same meanings as described above, instead of the compound represented by formula (II) and the compound represented by formula (V):



wherein all symbols have the same meanings as described above, instead of the compound represented by formula (III),

[0106] Moreover, the compound represented by formula (I-A) also can be prepared by the following esterification of the carboxylic acid derivative represented by formula (II) and the compound represented by formula (VI):



wherein Q is a halogen atom and R^2 has the same meaning as described above.

[0107] The esterification is known. The compound represented by formula (I) can be prepared, for example, by reacting the carboxylic acid derivative represented by formula (II) and the compound represented by formula (VI) in an organic solvent (e.g. dimethylformamide, dimethylacetamide, dimethylimidazole, tetrahydrofuran, ethyl ether, ethyl ether, dichloromethane, chloroform) in the presence of a base (e.g. potassium carbonate, sodium carbonate, cesium carbonate, sodium hydride, t-butoxypotassium, sodium methoxide, sodium ethoxide) at 0 to 100°C.

[0108] Moreover, the compound represented by formula (I-1) also can be prepared by the above reaction of the compound represented by formula (IV) and the compound represented by formula (VII):



wherein all symbols have the same meaning as described above.

[0109] The above esterification can be carried out either in the presence or absence of the inert gas such as argon or nitrogen.

[0110] In the above processes for the preparation, the compound represented by formula (II) or the compound represented by formula (IV) can be prepared by the methods described in WO03/74483 or the modified methods thereof.

[0111] The other test compounds is known or can be prepared easily by the combination of the known methods such as the methods described in Comprehensive Organic Transformations: A Guide to Functional Group Preparations, 2nd Edition (Richard C. Larock, John Wiley & Sons Inc, 1999) or Elmer J. Rauckman et al., J. Org. Chem., vol.41, No.3, 1976, p564-565.

[0112] In each reaction of the specification, the reactions with heating, as will be apparent to those skilled in the art, it may be carried with water bath, oil bath, sand bath and microwave.

[0113] In each reaction of the specification, it may be used a solid phase reagent which is supported by polymer (for example, polystyrene, polyacrylamide, polypropylene or polyethyleneglycol etc.).

[0114] In each reaction of the specification, the obtained products may be purified by conventional techniques. For example, the purification may be carried out by distillation at atmospheric or reduced pressure, by high performance liquid chromatography with silica gel or magnesium silicate, by thin layer chromatography, by ion-exchange resin, by scavenger resin, by column chromatography, by washing or by recrystallization. The purification may be done each reaction or after several reactions.

Toxicity

[0115] The toxicity of the compound represented by formula (I) is very low and therefore the compound may be considered safe for pharmaceutical use.

Application to pharmaceuticals

[0116] The pharmaceutical composition for inhalation comprising EP2 agonist has bronchodilating and antiinflammatory effects. Therefore, it is useful for preventing and/or treating respiratory diseases such as asthma, pulmonary injury (e.g. acute pulmonary injury, chronic pulmonary injury), pulmonary fibrosis, pulmonary emphysema, bronchitis (e.g. acute bronchitis, chronic bronchitis), chronic obstructive pulmonary disease, adult respiratory distress syndrome, cystic fibrosis or pulmonary hypertension. Moreover, the pharmaceutical composition for inhalation comprising a sustained produg of EP2 agonist is a safe and effective agent for preventing and/or treating respiratory diseases in which a desired effect such as a bronchodilating effect is sustained and a hypotensive effect is reduced.

[0117] The pharmaceutical composition for inhalation comprising the compound represented by formula (I) may be administered as a combined preparation by combining with other medicaments for the purpose of 1) supplementing and/or enhancing of prevention and/or treatment effect of the compound, 2) improvement in pharmacokinetics and

absorption and reduction of dose of the compound, and/or 3) reduction of side effect of the compound.

[0118] The compound represented by formula (I) and other medicaments may be administered in the form of combination preparation having these components incorporated in one preparation or may be administered in separate preparations. In the case where these medicaments are administered in separate preparations, they may be administered simultaneously or at different times. In the latter case, the medicament of the present invention may be administered before the other medicaments. Alternatively, the other medicaments may be administered before the medicament of the present invention. The method for the administration of these may be the same or different.

[0119] The other medicaments may be low-molecular compounds. In addition, they may be macromolecular protein, polypeptide, polynucleotide (DNA, RNA, and gene), antisense, decoy, antibody or vaccine and so on. The dose of the other medicaments can be accordingly selected as a standard of clinical dose. Additionally, the compounding ratio of EP₄ agonist of the present invention and the other medicaments can be accordingly selected by the age and body weight of administering object, the administration method, the administration time, the object disease, the symptom, the combination etc. For example, the other medicaments may be used from 0.0001 to 100 parts by weight relative to 1 part by weight of the medicament of the present invention. The other medicaments may be administered in combination, for example, any one or more compounds selected from the following same or different group at appropriate ratios. The other medicaments to compensate for and/or enhance the treatment effect of the compound represented by formula (I) do not only include ones which have ever been found but ones which will be found from now based on the above-mentioned mechanism.

[0120] The other medicaments include, for example, phosphodiesterase type 4 inhibitors, steroids, β agonists, leukotriene receptor antagonists, thromboxane synthase inhibitors, thromboxane A₂ receptor antagonists, mediator release inhibitors, antihistamines, xanthine derivatives, anticholinergic drugs, cytokine inhibitors, prostaglandins, forskolin preparations, elastase inhibitors, metalloproteinase inhibitors, expectorants, antibiotics or immunosuppressives etc.

[0121] Examples of phosphodiesterase type 4 inhibitors include rolipram, cilomilast, Bay19-8004, NIK-616, roflumilast (BY-217), cimapifylline (BRL-61063), Atizoram (CP-80633), SCH-351591, YM-976, V-11294A, PD-168787, D-4396, IC-485 or the like.

[0122] Examples of steroid include internal or injectable steroid such as cortisone acetate, hydrocortisone, hydrocortisone sodium phosphate, hydrocortisone sodium succinate, fludrocortisone acetate, prednisolone, prednisolone acetate, prednisolone sodium succinate, prednisolone butyrate, prednisolone sodium phosphate, halopredone acetate, methylprednisolone, methylprednisolone acetate, methylprednisolone sodium succinate, triamcinolone, triamcinolone acetate, triamcinolone acetonide, dexamethasone, dexamethasone acetate, dexamethasone sodium phosphate, dexamethasone palmitate, paramethasone acetate or betamethasone, inhalation steroid such as beclomethasone dipropionate, fluticasone propionate, budesonide, flunisolide, triamcinolone, ST-126P, ciclesonide, dexamethasone, mometasone furoate, prasterone sulfonate, deflazacort, methylprednisolone sultepanate, methylprednisolone sodium succinate.

[0123] Examples of β agonist include fenoterol hydrobromide, salbutamol sulfate, terbutaline sulfate, formoterol fumarate, salmeterol xinafoate, isoproterenol sulfate, orciprenaline sulfate, cloriprenaline sulfate, epinephrine, trimetoprolol hydrochloride, hexoprenaline mesyl sulfate, procaterol hydrochloride, tulobuterol hydrochloride, tulobuterol, pirbuterol hydrochloride, clenbuterol hydrochloride, mabuterol hydrochloride, ritodrine hydrochloride, bambuterol, dopexamine hydrochloride, meludrine tartrate, AR-C68397, levosalbutamol, KUR-1246, KUL-7211, AR-C89855, S-1319 or the like.

[0124] Examples of leukotriene receptor antagonist include pranlukast hydrate, montelukast, zafirlukast, seratrodist, MCC-847, KCA-757, CS-615, YM-158, L-740515, CP-195494, LM-1484, RS-635, A-93178, S-36496, BIL-284, ONO-4057 or the like.

[0125] Examples of thromboxane A₂ receptor antagonist include seratrodist, ramatroban, domitroban calcium hydrate, KT-2-962 or the like.

[0126] Examples of mediator release inhibitor include tranilast, sodium cromoglicate, amlexanox, repirinast, ibudilast, dazanolast, pemirolast potassium or the like.

[0127] Examples of antihistamine include ketotifen fumarate, mequitazine, azelastine hydrochloride, oxatomide, terfenadine, emedastine difumarate, epinastine hydrochloride, astemizole, ebastine, cetirizine hydrochloride, bepotastine, fexofenadine hydrochloride, loratadine, desloratadine, olopatadine hydrochloride, TAK-427, ZCR-2060, NIP-530, mometasone furoate, mizolastine, BP-294, andolast, auranofin, acrivastine or the like.

[0128] Examples of xanthine derivative include aminophylline, theophylline, dioxaphylline, cimapiphylline, diprophyllyne or the like.

[0129] Examples of anticholinergic drug include ipratropium bromide, oxitropium bromide, flutropium bromide, cimetroprum bromide, teriverine, tiotropium bromide, revatrope (UK-112166) or the like.

[0130] Examples of cytokine inhibitor include suplastat tosilate or the like.

[0131] Examples of elastase inhibitor include sivelestat, ONO-6818, MR-889, PBI-1101, EPHNE-4, R-665 or the like.

[0132] Examples of expectorant include foeniculated ammonia spirit, sodium bicarbonate, bromhexine hydrochloride, carbocisteine, ambroxol hydrochloride, sustained preparation of ambroxol hydrochloride, methylcysteine hydrochloride, acetylcysteine, L-cysteine ethyl ester hydrochloride, tyloxapol or the like.

[0133] Examples of antibiotic include cefuroxime sodium, meropenem trihydrate, netilmicin sulfate, sisomicin sulfate, cefibuten, PA-1806, IB-367, tobramycin, PA-1420, doxorubicin, astromicin sulfate, cefetamet pivoxil hydrochloride and the like. Examples of antibiotic for inhalation include PA-1806, IB-367, tobramycin, PA-1420, doxorubicin, astromicin sulfate, cefetamet pivoxil hydrochloride or the like.

[0134] Examples of immunosuppressive include cyclosporine, tacrolimus, azathioprine, methotrexate, cyclophosphamide or the like,

[0135] The other medicaments to compensate for and/or enhance the preventive and/or treatment effect of the compound represented by formula (I) do not only include ones which have ever been found but ones which will be found from now based on the above-mentioned mechanism.

[0136] The pharmaceutical composition for inhalation of the present invention can be produced by adding an additive permissible for pharmaceuticals, and by forming a preparation with a technology which is commonly utilized for a single preparation or a combination preparation to the compound represented by formula (I).

[0137] The pharmaceutical composition for inhalation of the present invention preferably shows a specific activity in the tissues around trachea such as bronchus, trachea and lung for the purpose of dose reduction and by-effect reduction.

[0138] The doses to be administered are differently determined depending upon, for example, age, body weight, symptom, the desired therapeutic effect, the route of administration, and the duration of the treatment etc. In the human adult, the doses per person are generally from 1 ng to 100 mg, by inhalation administration (via lung or airway), from one time to several times per day.

[0139] As mentioned above, the doses vary depending upon various conditions. Therefore, there are cases in which doses lower than the above described doses are enough or more administration is necessary greater doses than the ranges specified above.

[0140] The preparation forms of the pharmaceutical composition for inhalation of the present invention include inhalation preparations, such as an aerosol, an inhalation powder preparation, an inhalation liquid preparation such as inhalation solution, an inhalation suspension and the like, or an encapsulated inhalation preparation. Such inhalation liquid preparations may be in a form to be dissolved or suspended in water or another suitable solvent when they are used. Such inhalation preparations can be administered with an appropriate inhalation container, such as a sprayer (atomizer or nebulizer and the like) in case of an inhalation liquid preparation, or an inhalation administrator for powder preparation in case of an inhalation powder preparation.

[0141] Such inhalation preparations can be according to publicly known methods. For example, these can be produced by forming the compound represented by formula (I) into powder or liquid and blending it in an inhalation propellant and/or a carrier, followed by filling it in an appropriate inhalation container. In case of forming the compound represented by formula (I) into powder, it can be formed into powder according to the ordinary method. For example it is formed into fine powder with lactose, starch, magnesium stearate or the like to obtain a uniform mixture, or followed by granulation to obtain a powder preparation. Also in case of forming the compound represented by formula (I) into a liquid, said compound may be dissolved in a liquid carrier such as water, physiological saline or an organic solvent. As the propellant, an already known propellant such as substitute flon, a liquefied gas propellant such as fluorinated hydrocarbon, liquefied petroleum, diethyl ether, dimethyl ether and the like, a compressed gas such as a soluble gas such as carbon dioxide gas, nitrous oxide gas and the like or an insoluble gas such as nitrogen gas and the like, and the like can be used.

[0142] Furthermore, in the inhalation preparation, an additive may be suitably blended if necessary. The additive may be any additive which is ordinarily utilized and it may be for example a solid excipient such as white sugar, lactose, glucose, mannitol, sorbitol, maltose, cellulose and the like, a liquid filler such as propylene glycol and the like, a binder such as starch, dextrin, methylcellulose, hydroxypropylcellulose, polyvinylpyrrolidone, polyethylene glycol, white sugar and the like, a lubricant such as magnesium stearate, light silicic anhydride, talc, sodium laurylsulfate and the like, a taste-masking agent such as citric acid, menthol, ammonium glycyrrhizinate, glycine, orange powder, and the like, a preservative such as sodium benzoate, sodium hydrogensulfite, methylparaben, propylparaben and the like, a stabilizer such as citric acid, sodium citrate, and the like, a suspending agent or an emulsifier such as methylcellulose, polyvinylpyrrolidone, polyvinyl alcohol, lecithin, sorbitan trioleate and the like, a dispersant such as a surfactant and the like, a solvent such as water and the like, an isotonicizing agent such as sodium chloride, concentrated glycerin and the like, a pH regulating agent such as hydrochloric acid, sulfuric acid and the like, a solubilizing agent such as ethanol and the like, an antiseptic such as benzalkonium chloride, parabens and the like, a colorant, a buffer such as sodium phosphate, sodium acetate and the like, a viscosifier such as carboxyvinyl polymer and the like and an absorption promoter. For example, an inhalation liquid preparation is prepared by suitably selecting an antiseptic, a colorant, a buffer, an isotonicizing agent, a viscosifier, an absorption promoter and the like according to the necessity. Also an inhalation powder preparation is prepared by suitably selecting a lubricant, a binder, a filler, a colorant, an antiseptic, an absorption promoter such as a bile salt, chitosan and the like, and the like, according to the necessity.

[0143] Also in order to provide the compound represented by formula (I) with a sustained-release property, the inhalation preparation may contain a biodegradable polymer. Examples of the biodegradable polymer include a polymer or a copolymer of a fatty acid ester, a variety of polyacrylic acid ester, a variety of polyhydroxybutyric acid, a variety of

polyalkylene oxalate, polyorthoester, polycarbonate and a variety of polyamino acids, and these may be used singly or as a mixture of plural kinds. A phospholipid such as egg yolk lecithin or chitosan may be also used. Examples of the polymer or copolymer of fatty acid ester include poly(lactic acid), poly(glycolic acid), poly(citric acid), poly(malic acid) and a lactic acid-glycolic acid copolymer, and these may be used singly or as a mixture of plural kinds. Additionally, a poly- α -cyanoacrylic acid ester, poly- β -hydroxybutyric acid, poly(trimethylene oxalate), poly(orthoester), poly(orthocarbonate), poly(ethylene carbonate), poly- γ -benzyl-L-glutamic acid or poly-L-alanine may be used singly or in a mixture of plural kinds. Poly(lactic acid), poly(glycolic acid) or a lactic acid-glycolic acid copolymer is preferred, and a lactic acid-glycolic acid copolymer is more preferred. Additionally, microspheres or nanospheres incorporating an agent may be prepared by a biodegradable polymer such as lactic acid-glycolic acid copolymer and the like.

Examples

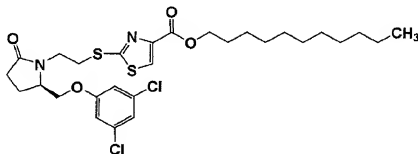
[0144] The present invention is explained below in detail based on Examples, but the present invention is not limited thereto.

[0145] In chromatographic separations and TLC, the solvents in parenthesis show the eluting and developing solvents and the ratios of the solvents used are by volume.

[0146] Unless otherwise specified, NMR data is ^1H -NMR data.

[0147] The solvents in parenthesis in NMR show the solvents used for measurement.

[0148] All the compounds described in the present specification were named using ACD/Name (registered trademark: Advanced Chemistry Development Inc.) or ACD/Name Batch (registered trademark: Advanced Chemistry Development Inc.) which names generally on the basis of IUPAC, or named according to IUPAC nomenclature system. For example, a compound represented by



was named undecyl 2-[(2-[(2R)-2-[(3,5-dichlorophenoxy)methyl]-5-oxo-1-pyrrolidinyl)ethyl]sulfanyl]-1,3-thiazole-4-carboxylate.

[0149] A carboxylic acid derivative used as the source material in Example is described in WO03/74483. For example, 2-[(2-[(2R)-2-[(3,5-dichlorophenoxy)methyl]-5-oxopyrrolidin-1-yl)ethyl]thio]-1,3-thiazole-4-carboxylic acid is prepared in Example 6(32) of WO03/74483.

Example 1 : 5-[(1 Z)-1-hepten-1-yl]-2-methylphenol

[0150] Under an atmosphere of Argon, to a solution of n-hexylphosphonium bromide (1.07 g) in tetrahydrofuran (10 mL) was added potassium t-butoxide (336 mg) at room temperature and the solution was stirred for 30 minutes. After cooling in ice bath, 3-hydroxy-4-methylbenzaldehyde (136 mg) was added to the reaction solution, which was stirred at room temperature for 1.5 hours. The reaction solution was diluted with t-butyl methyl ether. The solution was washed with dilute hydrochloric acid, water and brine, dried over anhydrous sodium sulfate and concentrated. The obtained residue was purified by column chromatography on silica gel (ethyl acetate : hexane = 1 : 4) to give the title compound (180 mg) having the following physical data.
TLC:Rf 0.63 (ethyl acetate : hexane = 1 : 4).

Example 2 : 5-heptyl-2-methylphenol

[0151] To a solution of the compound prepared in Example 1 (180 mg) in ethanol (5 mL) was added platinum-carbon (10 mg) and the solution was stirred at 60 °C for 7 hours under an atmosphere of hydrogen. After cooling to room temperature, the solution was filtrated through Celite (brand name) and washed with chloroform. The filtrate was concentrated to give the title compound (181 mg) having the following physical data.

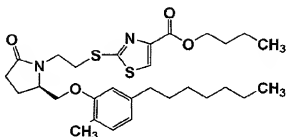
TLC : Rf 0.62 (ethyl acetate : hexane = 1 : 4).

Example 3: butyl 2-[(2-((2R)-2-[(methylsulfonyl)oxy]methyl]-5-oxo-1-pyrrolidinyl)ethyl)thio]-1,3-thiazole-4-carboxylate

[0152] To a solution of butyl 2-[(2-((2R)-2-(hydroxymethyl)-5-oxo-1-pyrrolidinyl)ethyl)thio]-1,3-thiazole-4-carboxylate (100 mg ; the compound described in Reference Example 19 of WO03/74483) and triethylamine (0.070 mL) in anhydrous tetrahydrofuran (3 mL) was cooled in ice under an atmosphere of Argon. Methane sulfonylchloride (0.026 mL) was added thereto and the solution was stirred for 30 minutes. The suspension was diluted with t-butyl methyl ether. The solution was washed dilute hydrochloric acid, water, a saturated aqueous sodium hydrogen carbonate solution and brine, dried over anhydrous sodium sulfate and concentrated to give the title compound (122 mg) having the following physical data. TLC : Rf 0.45 (ethyl acetate : hexane = 1 : 1).

Example 4 : butyl 2-[(2-((2R)-2-[(5-heptyl-2-methylphenoxy)methyl]-5-oxo-1-pyrrolidinyl)ethyl)thio]-1,3-thiazole-4-carboxylate

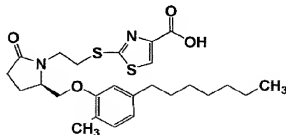
[0153]



[0154] To a solution of the compound prepared in Example 2 (31 mg) and the compound prepared in Example 3 (43 mg) in anhydrous dimethylformamide (2 mL) was added cesium carbonate (65 mg) and the solution was stirred at 60 °C overnight under an atmosphere of Argon. The reaction solution was diluted with t-butyl methyl ether. The solution was washed with dilute hydrochloric acid, water and brine, dried over anhydrous sodium sulfate and concentrated. The obtained residue was purified by column chromatography on silica gel (ethyl acetate : hexane = 1 : 4 → 1 : 1) to give the title compound (34 mg) having the following physical data. TLC : Rf 0.81 (ethyl acetate : hexane = 1 : 1).

Example 5 : 2-[(2-((2R)-2-[(5-heptyl-2-methylphenoxy)methyl]-5-oxo-1-pyrrolidinyl)ethyl)sulfany]-1,3-thiazole-4-carboxylic acid

[0155]



[0156] To a solution of the compound prepared in Example 4 (34 mg) in methanol (1 mL)-tetrahydrofuran (2mL) was added 2N aqueous sodium hydroxide solution (1 mL) at room temperature and the solution was stirred for 2 hours. The reaction solution was acidified with 1 N hydrochloric acid and extracted with ethyl acetate. The organic layer was washed with water and brine, dried over anhydrous sodium sulfate and concentrated to give the compound of the present invention

(28mg) having the following physical data.

TLC: Rf 0.36 (chloroform : methanol = 9 : 1);

NMR (CDCl₃): δ 0.78 - 0.95 (m, 3 H), 1.19 - 1.40 (m, 8 H), 1.47 - 1.67 (m, 2 H), 1.89 - 2.05 (m, 1 H), 2.16 (s, 3 H), 2.17 - 2.38 (m, J=20.22, 8.14 Hz, 1 H), 2.37 - 2.72 (m, 4 H), 3.15 - 3.33 (m, 1 H), 3.42 - 3.61 (m, J=13.17, 5.12 Hz, 1 H), 3.75 - 3.87 (m, 1 H), 3.87 - 4.05 (m, 2 H), 4.05 - 4.22 (m, 2 H), 6.61 (s, 1 H), 6.72 (d, J=7.50 Hz, 1 H), 7.05 (d, J=7.50 Hz, 1 H), 8.07 (s, 1 H).

Example 5(1)-(5)

[0157] By the same procedure as a series of reactions of Example 4→Example 5 using a corresponding alcohol derivative instead of the compound prepared in Example 2, the following compounds of the present invention were obtained.

Example 5(1): 2-[(2-((2R)-2-[(4-heptyl-2,6-dimethylphenoxy)methyl]-5-oxo-1-pyrrolidinyl)ethyl)sulfanyl]-1,3-thiazole-4-carboxylic acid

[0158] TLC: Rf 0.30 (chloroform : methanol = 9 : 1);

NMR (CDCl₃): δ 0.81 - 0.95 (m, 3 H), 1.17 - 1.39 (m, 8 H), 1.43 - 1.65 (m, 1 H), 1.83 - 2.07 (m, 2 H), 2.13 - 2.31 (m, 7 H), 2.31 - 2.68 (m, 4 H), 3.37 - 3.56 (m, 2 H), 3.59 - 3.80 (m, 2 H), 3.82 - 3.97 (m, 1 H), 4.01 - 4.30 (m, 2 H), 6.81 (s, 2 H), 8.08 (s, 1 H).

Example 5(2): 2-[(2-((2R)-2-[(4-chloro-2-heptylphenoxy)methyl]-5-oxo-1-pyrrolidinyl)ethyl)sulfanyl]-1,3-thiazole-4-carboxylic acid

[0159] TLC: Rf 0.30 (chloroform : methanol = 9 : 1);

NMR (CDCl₃): δ 0.79 - 0.95 (m, 3 H), 1.14 - 1.39 (m, 8 H), 1.42 - 1.63 (m, 2 H), 1.87 - 2.05 (m, 1 H), 2.17 - 2.35 (m, 1 H), 2.36 - 2.69 (m, 4 H), 3.13 - 3.33 (m, 1 H), 3.38 - 3.56 (m, 1 H), 3.62 - 3.82 (m, 1 H), 3.83 - 4.03 (m, 2 H), 4.03 - 4.22 (m, 2 H), 6.66 - 6.81 (m, 2 H), 7.03 - 7.17 (m, 2 H), 8.07 (s, 1 H).

Example 5(3): 2-[(2-((2R)-2-[(3-chloro-4-heptylphenoxy)methyl]-5-oxo-1-pyrrolidinyl)ethyl)sulfanyl]-1,3-thiazole-4-carboxylic acid

[0160] TLC: Rf 0.28 (chloroform : methanol = 9 : 1);

NMR (CDCl₃): δ 0.82 - 0.96 (m, 3 H), 1.18 - 1.41 (m, 8 H), 1.45 - 1.67 (m, 2 H), 1.84 - 2.02 (m, 1 H), 2.14 - 2.32 (m, 1 H), 2.34 - 2.50 (m, 1 H), 2.50 - 2.73 (m, 3 H), 3.15 - 3.35 (m, 1 H), 3.42 - 3.58 (m, 1 H), 3.76 (dd, J=10.34, 5.03 Hz, 1 H), 3.82 - 4.01 (m, 2 H), 4.00 - 4.19 (m, 2 H), 6.71 (dd, J=8.51, 2.65 Hz, 1 H), 8.88 (d, J=2.74 Hz, 1 H), 7.11 (d, J=8.42 Hz, 1 H), 8.08 (s, 1 H).

Example 5(4): 2-[(2-((2R)-2-[(2-chloro-4-heptylphenoxy)methyl]-5-oxo-1-pyrrolidinyl)ethyl)sulfanyl]-1,3-thiazole-4-carboxylic acid

[0161] TLC: Rf 0.25 (chloroform : methanol = 9 : 1);

NMR (CDCl₃): δ 0.89 - 0.94 (m, 3 H), 1.18 - 1.39 (m, 8 H), 1.44 - 1.66 (m, 2 H), 1.78 - 1.97 (m, 1 H), 2.17 - 2.35 (m, 1 H), 2.39 - 2.57 (m, 3 H), 2.56 - 2.73 (m, 1 H), 3.20 - 3.38 (m, 1 H), 3.48 - 3.65 (m, 1 H), 3.76 - 3.92 (m, 1 H), 3.92 - 4.08 (m, 2 H), 4.06 - 4.24 (m, 2 H), 6.80 (d, J=8.42 Hz, 1 H), 6.95 - 7.07 (m, 1 H), 7.17 - 7.24 (m, 1 H), 8.03 - 8.10 (m, 1 H).

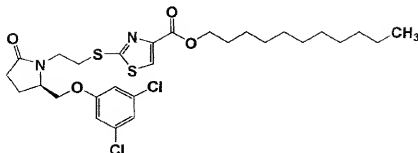
Example 5(5): 2-[(2-((2R)-2-[(4-heptyl-3,5-dimethylphenoxy)methyl]-5-oxo-1-pyrrolidinyl)ethyl)sulfanyl]-1,3-thiazole-4-carboxylic acid

[0162] TLC: Rf 0.48 (chloroform : methanol = 9 : 1);

NMR (CDCl₃): δ 0.82 - 0.96 (m, 3 H), 1.18 - 1.50 (m, 10 H), 1.83 - 2.01 (m, 1 H), 2.11 - 2.24 (m, 1 H), 2.28 (s, 6 H), 2.31 - 2.66 (m, 4 H), 3.17 - 3.34 (m, 1 H), 3.42 - 3.57 (m, 1 H), 3.67 - 3.83 (m, 1 H), 3.82 - 3.98 (m, 2 H), 3.98 - 4.17 (m, 2 H), 6.52 (s, 2 H), 8.06 (s, 1 H).

Example 6 : undecyl 2-[(2-((2R)-2-[(3,5-dichlorophenoxy)methyl]-5-oxo-1-pyrrolidinyl)ethyl)sulfanyl]-1,3-thiazole-4-carboxylate

[0163]



[0164] To a solution of 2-[(2-[(2R)-2-[(3,5-dichlorophenoxy)methyl]-5-oxopyrrolidin-1-yl)ethyl]thio]-1,3-thiazole-4-carboxylic acid (102 mg; the compound prepared in Example 6(32) of WO03/74483) and 1-bromoundecane (106 mg) in anhydrous dimethylformamide (5 mL) was added cesium carbonate (147 mg, 0.45 mmol) and the solution was stirred at 60°C for 3 hours under an atmosphere of Argon. The reaction solution was diluted with t-butyl methyl ether. The solution was washed with dilute hydrochloric acid, water and brine, dried over anhydrous sodium sulfate and concentrated. The obtained residue was purified by column chromatography on silica gel (ethyl acetate : hexane = 1 : 4 → 1 : 1) to give the compound of the present invention (131 mg) having the following physical data. TLC: Rf 0.46 (ethyl acetate : hexane = 1 : 1);

NMR (CDCl₃): δ 0.83 - 0.93 (m, 3 H), 1.16 - 1.47 (m, 16 H), 1.68 - 1.82 (m, 2 H), 1.98 - 2.13 (m, 1 H), 2.15 - 2.31 (m, 1 H), 2.32 - 2.47 (m, 1 H), 2.49 - 2.65 (m, 1 H), 3.20 - 3.34 (m, 1 H), 3.40 - 3.54 (m, 1 H), 3.54 - 3.68 (m, 1 H), 3.76 - 3.92 (m, 1 H), 4.00 (dd, J=10.43, 3.29 Hz, 1 H), 4.07 - 4.18 (m, 1 H), 4.25 - 4.40 (m, 2 H), 4.68 (dd, J=10.34, 3.02 Hz, 1 H), 6.84 - 6.89 (m, 2 H), 6.91 - 6.95 (m, 1 H), 7.97 (s, 1 H).

Example 6(1)-(3)

[0165] By the same procedure as a series of reactions of Example 6 using a corresponding carboxylic acid derivative instead of 2-[(2-[(2R)-2-[(3,5-dichlorophenoxy)methyl]-5-oxopyrrolidin-1-yl)ethyl]thio]-1,3-thiazole-4-carboxylic acid, and a corresponding bromide or iodide instead of 1-bromoundecane, the following compounds of the present invention were obtained.

Example 6(1): 10-phenyldecyl 2-[(2-[(2R)-2-[(3,5-dichlorophenoxy)methyl]-5-oxo-1-pyrrolidinyl)ethyl]sulfonyl]-1,3-thiazole-4-carboxylate

[0166] TLC: Rf 0.41 (ethyl acetate : hexane = 1 : 1);

NMR (CDCl₃): δ 1.21 - 1.46 (m, 12 H), 1.53 - 1.68 (m, 2 H), 1.68 - 1.81 (m, 2 H), 1.97 - 2.13 (m, 1 H), 2.13 - 2.30 (m, 1 H), 2.30 - 2.46 (m, 1 H), 2.50 - 2.66 (m, 3 H), 3.19 - 3.35 (m, 1 H), 3.40 - 3.53 (m, 1 H), 3.54 - 3.68 (m, 1 H), 3.77 - 3.91 (m, 1 H), 4.00 (dd, J=10.34, 3.20 Hz, 1 H), 4.06 - 4.18 (m, 1 H), 4.26 - 4.40 (m, 2 H), 4.68 (dd, J=10.25, 2.93 Hz, 1 H), 6.87 (d, J=1.65 Hz, 2 H), 6.92 (t, J=1.83 Hz, 1 H), 7.13 - 7.21 (m, 3 H), 7.23 - 7.31 (m, 2 H), 7.97 (s, 1 H).

Example 6(2): 10-phenyldecyl 2-[(2-[(5R)-2-oxo-5-[(3-(trifluoromethoxy)phenoxy)methyl]-1-pyrrolidinyl)ethyl]sulfonyl]-1,3-thiazole-4-carboxylate

[0167] TLC: Rf 0.47 (ethyl acetate : hexane = 1 : 1);

NMR (CDCl₃): δ 1.20 - 1.46 (m, 12 H), 1.50 - 1.66 (m, 2 H), 1.66 - 1.84 (m, 2 H), 1.97 - 2.15 (m, 1 H), 2.15 - 2.31 (m, 1 H), 2.30 - 2.47 (m, 1 H), 2.48 - 2.68 (m, 3 H), 3.23 - 3.40 (m, 1 H), 3.41 - 3.68 (m, 2 H), 3.80 - 3.95 (m, 1 H), 4.02 (dd, J=10.25, 3.48 Hz, 1 H), 4.08 - 4.21 (m, 1 H), 4.30 (t, J=6.77 Hz, 2 H), 4.56 (dd, J=10.43, 3.11 Hz, 1 H), 6.73 - 6.90 (m, 3 H), 7.10 - 7.34 (m, 6 H), 7.96 (s, 1 H).

Example 6(3): 10-phenyldecyl 2-[(2-[(2R)-2-[(1 E,4S)-4-(1-ethylcyclobutyl)-4-hydroxy-1-buten-1-yl]-5-oxo-1-pyrrolidinyl)ethyl]sulfonyl]-1,3-thiazole-4-carboxylate

[0168] TLC: Rf 0.32 (hexane : ethyl acetate = 1 : 2);

NMR (CDCl₃): δ 0.90 (t, J=7.50 Hz, 3 H), 1.24 - 1.47 (m, 11 H), 1.54 - 2.04 (m, 17 H), 2.13 - 2.48 (m, 4 H), 2.56 - 2.63 (m, 2 H), 3.35 - 3.56 (m, 4 H), 3.72 - 3.89 (m, 1 H), 4.14 - 4.24 (m, 1 H), 4.31 (t, J=6.90 Hz, 1 H), 5.39 (dd, J=15.40, 8.90 Hz, 1 H), 5.82 (dt, J=15.40, 7.00 Hz, 1 H), 7.13 - 7.21 (m, 3 H), 7.23 - 7.31 (m, 2 H), 7.99 (s, 1 H).

Example 7 : 2-{{2-[(2R)-2-{{(tert-butyl(dimethyl)silyl)oxy)methyl}-5-oxo-1-pyrrolidinyl]ethyl}thio}-1,3-thiazole-4-carboxylic acid

[0169] To a solution of 2-{{2-[(2R)-2-(t-butyl(dimethyl)silyloxy)methyl]-5-oxopyrrolidin-1-yl]ethylthio}-1,3-thiazole-4-carboxylic acid ethyl ester (240 mg ; the compound described in Reference Example 17 of WO03/74483) in tetrahydrofuran (4 mL)-methanol (2 mL) was added 2N aqueous sodium hydroxide solution (2 mL) at room temperature and the solution was stirred for 1 hour. The reaction solution was acidified with dilute hydrochloric acid and extracted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous sodium sulfate and concentrated to give the title compound (240 mg) having the following physical data.

TLC : Rf 0.10 (chloroform : methanol = 9 : 1).

Example 8 : 10-phenyldecyl 2-{{2-[(2R)-2-{{(tert-butyl(dimethyl)silyl)oxy)methyl}-5-oxa-1-pyrrolidinyl]ethyl}thio}-1,3-thiazole-4-carboxylate

[0170] To a solution of the compound prepared in Example 7 (240 mg) and 10-iododecylbenzene (261 mg) in anhydrous dimethylformamide (5 mL) was added cesium carbonate (315 mg) and the solution stirred at 50°C overnight under an atmosphere of Argon. The reaction solution was diluted with tert-butoxymethyl. The solution was washed with dilute hydrochloric acid, water and brine, dried over anhydrous sodium sulfate and concentrated to give the title compound (430 mg) having the following physical data.

TLC : Rf 0.87 (ethyl acetate).

Example 9 : 10-phenyldecyl 2-{{2-[(2R)-2-(hydroxymethyl)-5-oxo-1-pyrrolidinyl]ethyl}thio}-1,3-thiazole-4-carboxylate

[0171] To a solution of the compound prepared in Example 8 (430 mg) in tetrahydrofuran (3 mL) was added a solution of tetrabutylammonium fluoride in tetrahydrofuran (1.0 M, 1.1 mL) at room temperature and the solution was stirred for 1 hour. The reaction solution was diluted with ethyl acetate. The solution was washed with a saturated ammonium chloride solution and brine, dried over anhydrous sodium sulfate and concentrated. The obtained residue was purified by column chromatography on silica gel (ethyl acetate : hexane = 1 : 1 → 1 : 0) to give the title compound (195 mg) having the following physical data.

TLC : Rf 0.28 (ethyl acetate).

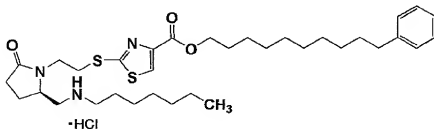
Example 10 : 10-phenyldecyl 2-{{2-[(2R)-2-formyl-5-oxo-1-pyrrolidinyl]ethyl}thio}-1,3-thiazole-4-carboxylate

[0172] Under an atmosphere of Argon, a solution of the compound prepared in Example 9 (195 mg) and diisopropylethylamine (0.39 mL) in ethyl acetate (2 mL)-dimethylsulfoxide (1 mL) was cooled to 0°C. Sulfur trioxide-pyridine complex (180 mg) was added to the solution, which was stirred for 1 hour. The reaction solution was diluted with ethyl acetate. The solution was washed with dilute hydrochloric acid, water and brine, dried over anhydrous sodium sulfate and concentrated to give the title compound (200 mg) having the following physical data.

TLC : Rf 0.50 (ethyl acetate : methanol = 19 : 1).

Example 11 : 10-phenyldecyl 2-{{2-[(2R)-2-{{(heptylamino)methyl}-5-oxo-1-pyrrolidinyl]ethyl}sulfanyl]-1,3-thiazole-4-carboxylate hydrochloride

[0173]



[0174] Under an atmosphere of Argon, to a solution of the compound prepared in Example 10 (200 mg) in dichloromethane (4 mL) was added heptylamine (0.11 mL) at room temperature and the solution was stirred for 1 hour. Sodium

triacetoxyborohydride (159 mg) was added to the reaction solution, which was stirred for 2 hours. After the reaction was stopped by adding a saturated aqueous sodium hydrogen carbonate solution, the reaction mixture was poured into water and extracted with ethyl acetate. The reaction mixture was washed with brine, dried over anhydrous sodium sulfate and concentrated. The obtained residue was purified by column chromatography on silica gel (chloroform : methanol = 100 : 1 → 30 : 1). The obtained oil was dissolved in ethyl acetate. 4N hydrogen chloride/ethyl acetate solution (0.1 mL) was added thereto. The mixture was concentrated to give the compound of the present invention (195 mg) having the following physical data.

TLC : Rf 0.55 (chloroform : methanol = 9 : 1);

NMR (CD₃OD) : δ 0.85 - 0.97 (m, 3 H), 1.23 - 1.50 (m, 20 H), 1.59 (s, 2 H), 1.67 - 1.84 (m, 4 H), 1.98 (d, J=16.28 Hz, 1 H), 2.23 - 2.51 (m, 3 H), 2.53 - 2.63 (m, 2 H), 3.03 - 3.23 (m, J=7.68 Hz, 4 H), 3.44 - 3.58 (m, J=9.70 Hz, 2 H), 3.60 - 3.71 (m, 1 H), 3.76 - 3.91 (m, J=7.87 Hz, 1 H), 4.10 - 4.22 (m, 1 H), 4.32 (t, J=6.68 Hz, 2 H), 7.01 - 7.42 (m, 5 H), 8.29 (s, 1 H).

Example 11(1): undecyl 2-[(2-[(2R)-2-[(heptylamino)methyl]-5-oxo-1-pyrrolidinyl)ethyl)sulfanyl]-1,3-thiazole-4-carboxylate hydrochloride

[0175] By the same procedure as a series of reactions of Example 8 → Example 9 → Example 10 → Example 11 using 1-bromoundecane instead of 10-iododecylbenzene, the compound of the present invention having the following physical data was obtained.

TLC : Rf 0.19 (chloroform : methanol = 9 : 1);

NMR (CD₃OD) : δ 0.82 - 0.99 (m, 6 H), 1.22 - 1.50 (m, 24 H), 1.68 - 1.85 (m, 4 H), 1.87 - 2.05 (m, 1 H), 2.22 - 2.54 (m, 3 H), 3.02 - 3.28 (m, 4 H), 3.43 - 3.61 (m, 2 H), 3.67 (dd, J=12.81, 2.93 Hz, 1 H), 3.76 - 3.95 (m, 1 H), 4.17 (s, 1 H), 4.28 - 4.39 (m, 2 H), 8.16-8.42 (m, 1 H).

Example 12(1)-(3)

[0176] By the same procedure as a series of reactions of Example 6 using 2-[(2-[(2R)-2-[(3,5-dichlorophenoxy)methyl]-5-oxopyrrolidin-1-yl)ethyl]thio]-1,3-thiazole-4-carboxylic acid or 2-[(2-[(2R)-2-[(1 E)-1-nonenyl]-5-oxo-1-pyrrolidinyl)ethyl)sulfanyl]-1,3-thiazole-4-carboxylic acid, and a corresponding bromide or iodide instead of 1-bromoundecane, the following compounds of the present invention were obtained.

Example 12(1): 10-phenyldecyl 2-[(2-[(2R)-2-[(1 E)-1-nonenyl]-5-oxo-1-pyrrolidinyl)ethyl)sulfanyl]-1,3-thiazole-4-carboxylate

[0177] TLC: Rf 0.49 (hexane : ethyl acetate = 1 : 1);

NMR (CDCl₃) : δ 0.88 (t, J=6.60 Hz, 3 H) 1.16 - 1.46 (m, 21 H) 1.54 - 1.82 (m, 6 H) 1.93 - 2.03 (m, 2 H) 2.12 - 2.46 (m, 3 H) 2.60 (t, J=7.50 Hz, 2 H) 3.24 - 3.36 (m, 1 H) 3.37 - 3.52 (m, 2 H) 3.78 - 3.88 (m, 1 H) 4.09 - 4.19 (m, 1 H) 4.32 (t, J=6.90 Hz, 2 H) 5.16 - 5.27 (ddt, J=15.20, 9.00, 1.50 Hz, 1 H) 5.66 (dt, J=15.20, 6.80 Hz, 1 H) 7.13 - 7.21 (m, 3 H) 7.23 - 7.31 (m, 2 H) 8.00 (s, 1 H).

Example 12(2): 2-(decanoyloxy)ethyl 2-[(2-[(2R)-2-[(3,5-dichlorophenoxy)methyl]-5-oxo-1-pyrrolidinyl)ethyl)sulfanyl]-1,3-thiazole-4-carboxylate

[0178] TLC: Rf 0.20 (ethyl acetate : hexane = 1 : 1);

NMR (CDCl₃) : δ 0.82 - 0.92 (m, 3 H) 1.17 - 1.37 (m, 12 H) 1.54 - 1.68 (m, 2 H) 1.99 - 2.14 (m, 1 H) 2.15 - 2.28 (m, 1 H) 2.32 (t, J=7.50 Hz, 2 H) 2.36 - 2.47 (m, 1 H) 2.50 - 2.66 (m, 1 H) 3.19 - 3.32 (m, 1 H) 3.40 - 3.54 (m, 1 H) 3.54 - 3.68 (m, 1 H) 3.77 - 3.90 (m, 1 H) 4.00 (dd, J=10.34, 3.20 Hz, 1 H) 4.06 - 4.16 (m, 1 H) 4.33 - 4.48 (m, 2 H) 4.52 (q, J=4.45 Hz, 2 H) 4.68 (dd, J=10.25, 2.93 Hz, 1 H) 6.87 (d, J=1.83 Hz, 2 H) 6.92 (t, J=1.83 Hz, 1 H) 7.99 (s, 1 H).

Example 12(3) : 10-hydroxydecyl 2-[(2-[(2R)-2-[(3,5-dichlorophenoxy)methyl]-5-oxo-1-pyrrolidinyl)ethyl)sulfanyl]-1,3-thiazole-4-carboxylate

[0179] TLC : Rf 0.32 (ethyl acetate);

NMR (CDCl₃) : δ 1.22 - 1.46 (m, 16 H) 1.69 - 1.83 (m, 2 H) 1.94 - 2.15 (m, 1 H) 2.15 - 2.47 (m, 2 H) 2.48 - 2.68 (m, 1 H) 3.19 - 3.35 (m, 1 H) 3.35 - 3.55 (m, 1 H) 3.64 (t, J=6.59 Hz, 2 H) 3.77 - 3.94 (m, 1 H) 4.01 (dd, J=10.43, 3.11 Hz, 1 H) 4.08 - 4.20 (m, 1 H) 4.27 - 4.40 (m, 2 H) 4.68 (dd, J=10.25, 3.11 Hz, 1 H) 6.87 (d, J=1.83 Hz, 2 H) 6.93 (t, J=1.74 Hz, 1 H) 7.98 (s, 1 H).

Biological Example

(1) Inhibitory activity on histamine-induced airway contractile response and hypotensive activity of intravenous administration or inhalation administration in guinea pig

[0180] A guinea pig anesthetized with sodium pentobarbital (75 mg/kg, i.p.) was treated with gallamine (10 mg/kg, i.v.), and an experiment was carried out under artificial respiration. As an airway contraction inducing substance, histamine (10 µg/kg, i.v.) was used, and the airway contractile response was determined by the Konzett & Roessler method (Konzett, H., Roessler, R. Versuchsordnung zu untersuchungen an der Bronchial- muskulatur. Arch Exp Pathol Pharmacol 1940; 195: 71-74). Additionally, the blood pressure was also measured at the same time. A test substance was administered intravenously or by inhalation (the test substance or a physiological saline solution was atomized using an ultrasonic nebulizer and inhaled directly into the trachea for 5 minutes using an artificial respirator). An inhibition ratio of airway contraction (%) was calculated by taking the airway contraction induced by histamine before administration of the test substance or in a group administered with a physiological saline solution as 0% inhibition. The amount of blood pressure reduction (mmHg) was expressed as the amount of diastolic blood pressure reduction. The results are shown in Fig. 1. In the case of 2-[(2-[(2R)-2-[(1E,4S)-4-(1-ethylcyclobutyl)-4-hydroxybut-1-enyl]-5-oxopyrrolidin-1-yl)ethyl]sulfonyl]-1,3-thiazole-4-carboxylic acid (a compound described in Example 2 in WO 03/74483, hereinafter abbreviated as Compound A); 2-[(2-[(2R)-2-[(3,5-dichlorophenoxy)methyl]-5-oxopyrrolidin-1-yl)ethyl]thio]-1,3-thiazole-4-carboxylic acid (a compound described in Example 6(32) in WO 03/74483, hereinafter abbreviated as Compound B); 2-[(2-[(2R)-2-[(2-chloro-3-(trifluoromethyl)phenoxy)methyl]-5-oxopyrrolidin-1-yl)ethyl]sulfonyl]-1,3-thiazole-4-carboxylic acid (a compound described in Example 6(66) in WO 03/74483, hereinafter abbreviated as Compound C); and 2-[(2-[(5R)-2-oxo-5-[(3-(trifluoromethoxy)phenoxy)methyl]pyrrolidin-1-yl)ethyl]sulfonyl)-1,3-thiazole-4-carboxylic acid (a compound described in Example 6(74) in WO 03/74483, hereinafter abbreviated as Compound D), which are the pharmaceutical compositions for inhalation of the present invention, a dissociation between the inhibitory effect on airway contraction and the hypotensive effect became larger by inhalation administration than by intravenous administration. From this, it was shown that the pharmaceutical composition for inhalation of the present invention has an inhibitory effect on airway contraction and its hypotensive effect is small.

(2) Effect of compound of the present invention by intratracheal administration on methacholine-induced airway contractile response in guinea pig

[0181] A test substance was intratracheally administered to a guinea pig anesthetized with GOI (laughing gas : oxygen = 3 : 1, 3% isoflurane) using a tube for intratracheal administration. After a certain period of time, the guinea pig was anesthetized with sodium pentobarbital (50 mg/kg, i.p.) and treated with gallamine (10 mg/kg, i.v.). Then, the resulting airway contractile response was determined under artificial respiration. As an airway contraction inducing substance, methacholine (10 µg/kg, i.v.) was used, and the airway contractile response was determined by the Konzett & Roessler method. A ratio of airway contraction (% of maximum) was calculated by taking the airway response obtained by closing a three-way stopcock attached to an upper part of a cannula inserted into the tracheal tube of the guinea pig as 100%. The results are shown in Figs. 2 to 5. Although Compound B which is an EP2 agonist having a carboxyl group has a bronchodilator effect, the effect was lost at around 3 hours after the administration. On the other hand, butyl 2-[(2-[(2R)-2-[(3,5-dichlorophenoxy)methyl]-5-oxopyrrolidin-1-yl)ethyl]thio]-1,3-thiazole-4-carboxylate (a compound described in Example 5(32) in WO 03/74483, hereinafter abbreviated as Compound E), which is a butyl ester of Compound B, showed a more prolonged duration of activity compared with Compound B. Additionally, undecyl 2-[(2-[(2R)-2-[(3,5-dichlorophenoxy)methyl]-5-oxopyrrolidin-1-yl)ethyl]sulfonyl)-1,3-thiazole-4-carboxylate (a compound described in Example 6, hereinafter abbreviated as Compound F), or 10-phenyldecyl 2-[(2-[(2R)-2-[(3,5-dichlorophenoxy)methyl]-5-oxopyrrolidin-1-yl)ethyl]sulfonyl)-1,3-thiazole-4-carboxylate (a compound described in Example 6(1), hereinafter abbreviated as Compound G), which are a longer chain ester, showed a more prolonged duration of activity compared with Compound F. From this, it was shown that the pharmaceutical composition for inhalation with high lipid solubility has a more prolonged duration of activity.

(3) Bronchodilator effect and hypotensive effect of a sustained prodrug of EP2 agonist

[0182] A guinea pig anesthetized with sodium pentobarbital (50 mg/kg, i.p.) was treated with gallamine (10 mg/kg, i.v.), and an experiment was carried out under artificial respiration. As an airway contraction inducing substance, methacholine (10 µg/kg, i.v.) was used, and the airway contractile response was determined by the Konzett & Roessler method. Compound B was dissolved in an equimolar amount of sodium hydroxide and diluted with a physiological saline solution. Compound F was suspended in a physiological saline solution containing 2% ethanol and 10% Tween 80 to prepare a test substance. The test substance was intratracheally administered using a tube for intratracheal administration.

tration. After the administration of the test substance, the blood pressure and the airway contractile response were measured for 12.5 minutes and 3 hours, respectively. A ratio of airway contraction (%) was calculated by taking the airway response obtained by closing a three-way stopcock attached to an upper part of a cannula inserted into the tracheal tube of the guinea pig as 100% contraction. The amount of blood pressure reduction (mmHg) was expressed based on the blood pressure before administration of the test substance. The results are shown in Figs. 6 to 9. Compound F, which is an undecyl ester of Compound B, did not change the blood pressure and showed a prolonged duration of bronchodilator activity compared with Compound B. From this, it was shown that the sustained prodrug has a long duration of a bronchodilator effect, which is a main effect, and can reduce a hypotensive effect.

Formulation Example

[0183] The typical formulation example used in the present invention was described below.

Formulation Example 1:

[0184] The following constituent was mixed to give a solution for inhalation.

- compound F(undecyl 2-[(2-((2R)-2-[(3,5-dichlorophenoxy)methyl]-5-oxopyrrolidin-1-yl)ethyl)sulfanyl]-1,3-thiazole-4-carboxylate)(40mg)
- purified water (1000mL)

Formulation Example 2

[0185] After the compound F (5.6 g) and maltose (400g) was dissolved into purified water, to the mixture was added di-sodium hydrogen phosphate 12-hydrate (20 g) and thereto was added distilled water to fill up to 4000 mL. The solution was freeze-dried by a conventional method and crushed to give a powder for inhalation.

Industrial Applicability

[0186] A medicinal composition for inhalation containing a sustained prodrug of an EP2 agonist topically exhibits a prolonged bronchodilating and antiinflammatory effects. Namely, the pharmaceutical composition for inhalation containing a sustained prodrug of an EP2 agonist is useful as a safe preventive and/or treatment agent for respiratory diseases (for example, asthma, pulmonary injury such as acute pulmonary injury and chronic injury, pulmonary fibrosis, pulmonary emphysema, bronchitis such as acute bronchitis and chronic bronchitis, chronic obstructive pulmonary disease, adult respiratory distress syndrome, cystic fibrosis, pulmonary hypertension or the like) without causing any systemic effect such as blood pressure reduction.

Brief Description of the Drawings

[0187]

[Fig. 1] Inhibitory effect on airway contraction and hypotensive effect of the pharmaceutical composition of the present invention in intravenous administration or inhalation are indicated.

[Fig. 2] Inhibitory effect on airway contraction and the duration of effect of the compound B are indicated.

[Fig. 3] Inhibitory effect on airway contraction and the duration of effect of the compound E are indicated.

[Fig. 4] Inhibitory effect on airway contraction and the duration of effect of the compound F are indicated.

[Fig. 5] Inhibitory effect on airway contraction and the duration of effect of the compound G are indicated.

[Fig. 6] The alteration of blood by the compound B is indicated.

[Fig. 7] Inhibitory effect on airway contraction and the duration of effect of the compound B are indicated.

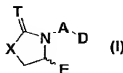
[Fig. 8] The alteration of blood pressure by the compound F is indicated.

[Fig. 9] Inhibitory effect on airway contraction and the duration of effect of the compound F are indicated.

Claims

1. A pharmaceutical composition for inhalation comprising EP2 agonist.
2. The pharmaceutical composition according to claim 1, wherein the EP2 agonist is a sustained prodrug.

3. The pharmaceutical composition according to claim 2, wherein the prodrug has reduced hypotensive effect.
4. The pharmaceutical composition according to claim 2, wherein the prodrug is an ester of a long chain aliphatic alcohol or an amide of a long chain aliphatic amine.
5. The pharmaceutical composition according to claim 1, wherein the EP2 agonist is a compound represented by formula (1):



wherein T is (1) an oxygen atom or (2) a sulfur atom,

X is (1) -CH₂- (2) -O- or (3) -S-,

A is A¹ or A²,

A¹ is (1) C2-8 straight-chain alkylene optionally substituted by 1 to 2 C1-4 alkyl, (2) C2-8 straight-chain alkenylene optionally substituted by 1 to 2 C1-4 alkyl or (3) C2-8 straight-chain alkynylene optionally substituted by 1 to 2 C1-4 alkyl,

A² is -G¹-G²-G³,

G¹ is (1) C1-4 straight-chain alkylene optionally substituted by 1 to 2 C1-4 alkyl, (2) C2-4 straight-chain alkenylene optionally substituted by 1 to 2 C1-4 alkyl or (3) C2-4 straight-chain alkynylene optionally substituted by 1 to 2 C1-4 alkyl,

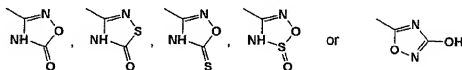
G² is (1) -Y-, (2)-ring 1-, (3) -Y-ring 1-, (4) -ring 1-Y- or (5) -Y-C1-4 alkylene-ring 1-,

Y is (1) -S-, (2) -SO-, (3) -SO₂-, (4) -O- or (5)-NR¹-,

R¹ is (1) a hydrogen atom, (2) C1-10 alkyl or (3) C2-10 acyl,

G³ is (1) a bond, (2) C1-4 straight-chain alkylene optionally substituted by 1 to 2 C1-4 alkyl, (3) C2-4 straight-chain alkenylene optionally substituted by 1 to 2 C1-4 alkyl or (4) C2-4 straight-chain alkynylene optionally substituted by 1 to 2 C1-4 alkyl,

D is (1) -COOH, (2) -COOR², (3) tetrazol-5-yl, (4) -CONR³SO₂R⁴, (5)-CH₂OH (6) -CH₂OR⁵, (7) hydroxy, (8) -OR⁵, (9) formyl, (10) -CONR⁶R⁷, (11) -CONR⁸OR⁹, (12) -CO-(NH-amino acid residue-CO)_m-OH, (13) -O-(CO-amino acid residue-NH)_m-H, (14) -OCO-R¹⁰, (15) -COO-Z¹-Z²-Z³ or (16)



R² is hydrocarbon which may have a substituent(s),

R³ is (1) a hydrogen atom or (2) a hydrocarbon which may have a substituent(s),

R⁴ is a hydrocarbon which may have a substituent(s),

R⁵ is a hydrocarbon which may have a substituent(s),

R⁶ and R⁷ are each independently (1) a hydrogen atom or (2) a hydrocarbon which may have a substituent(s),

R⁸ and R⁹ are each independently (1) a hydrogen atom or (2) a hydrocarbon which may have a substituent(s),

R¹⁰ is a hydrocarbon which may have a substituent(s),

m is 1 or 2,

Z¹ is (1) C1-15 alkenylene, (2) C2-15 alkenylene, or (3) C2-15 alkynylene,

Z² is (1) -CO-, (2) -OCO-, (3) -COO-, (4) -CONR²¹-, (5) -NR²²CO-, (6) -O-, (7) -S-, (8) -SO₂-, (9) -SO₂-NR²²-, (10) -NR²²SO₂-, (11) -NR²³-, (12) -NR²⁴CONR²⁵-, (13) -NR²⁶COO-, (14) -OCONR²⁷- or (15) -OCOO-,

Z³ is (1) a hydrogen atom, (2) C1-15 alkyl, (3) C2-15 alkenyl, (4) C2-15 alkynyl, (5) ring Z or (6) C1-10 alkyl substituted by C1-10 alkoxy, C1-10 alkylthio, C1-10 alkyl-NR²⁸- or ring Z,

ring Z is (1) a cyclic hydrocarbon, or (2) a heterocyclic ring,

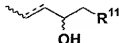
R²¹, R²², R²³, R²⁴, R²⁵, R²⁶, R²⁷ and R²⁸ are each independently a hydrogen atom or C1-15 alkyl.
 R²¹ and R²³ may be taken together with the nitrogen atom to which they are attached to form a 5 to 7 membered nitrogen-containing heterocyclic ring, and the heterocyclic ring may contain other 1 to 3 hetero atom(s) selected from oxygen, nitrogen and sulfur atoms,

ring Z and 5 to 7 membered nitrogen-containing heterocyclic ring formed by R²¹ and R²³ together with the nitrogen atom to which they are attached may be substituted by 1 to 3 group(s) selected from the following (1) to (4); (1) C1-15 alkyl, (2) C2-15 alkenyl, (3) C2-15 alkynyl, (4) C1-10 alkyl substituted by C1-10 alkoxy, C1-10 alkylthio or C1-10 alkyl-NR²⁹;

R²⁹ is a hydrogen atom or C1-10 alkyl,

E is E¹ or E²

E¹ is



R¹¹ is (1) C1-10 alkyl, (2) C1-10 alkylthio, (3) C1-10 alkyl substituted by C3-8 cycloalkyl, (4) C1-10 alkyl substituted by ring 2 or (5) C1-10 alkyl substituted by -W¹-W²-ring 2,

W¹ is (1) -O-, (2) -S-, (3) -SO-, (4) -SO₂-, (5) -NR¹¹⁻¹-, (6) carbonyl, (7) -NR¹¹⁻¹-SO₂-, (8) carbonylamino or (9) aminocarbonyl,

R¹¹⁻¹ is (1) a hydrogen atom, (2) C1-10 alkyl or (3) C2-10 acyl,

W² is (1) a bond or (2) C1-8 alkyl optionally substituted by C1-4 alkyl, a halogen atom or hydroxy,

E² is (1) -U¹-U²-U³ or (2) ring 4,

U¹ is (1) C1-4 alkylene, (2) C2-4 alkenylene, (3) C2-4 alkynylene, (4) -ring 3-, (5) C1-4 alkylene-ring 3-, (6) C2-4 alkenylene-ring 3- or (7) C2-4 alkynylene-ring 3-,

U² is (1) a bond, (2) -CH₂-, (3) -CHOH-, (4) -O-, (5) -S-, (6) -SO-, (7) -SO₂-, (8) -NR¹²⁻, (9) carbonyl, (10) -NR¹²-SO₂-, (11) carbonylamino or (12) aminocarbonyl,

R¹² is (1) a hydrogen atom, (2) C1-10 alkyl or (3) C2-10 acyl,

U³ is (1) C1-8 alkyl optionally substituted by 1 to 3 substituent(s) selected from C1-10 alkyl, halogen atom, hydroxy, C1-10 alkoxy, C1-10 alkylthio and NR¹³R¹⁴, (2) C2-8 alkenyl optionally substituted by 1 to 3 substituent(s) selected from C1-10 alkyl, a halogen atom, hydroxy, C1-10 alkoxy, C1-10 alkylthio and NR¹³R¹⁴, (3) C2-8 alkynyl optionally substituted by 1 to 3 substituent(s) selected from C1-10 alkyl, a halogen atom, hydroxy, C1-10 alkoxy, C1-10 alkylthio and NR¹³R¹⁴, (4) C1-8 alkyl substituted by ring 4 or (5) ring 4,

R¹³ and R¹⁴ are each independently (1) a hydrogen atom or (2) C1-10 alkyl, ring 1, ring 2, ring 3 and ring 4 are each independently optionally substituted by 1 to 5 R,

R is (1) C1-10 alkyl, (2) C2-10 alkenyl, (3) C2-10 alkynyl, (4) C1-10 alkoxy, (5) C1-10 alkylthio, (6) halogen atom, (7) hydroxy, (8) nitro, (9) -NR¹⁵R¹⁶, (10) C1-10 alkyl substituted by C1-10 alkoxy, (11) C1-10 alkyl substituted by 1 to 3 halogen atom(s), (12) C1-90 alkyl substituted by C1-10 alkoxy substituted by 1 to 3 halogen atom(s), (13) C1-10 alkyl substituted by -NR¹⁵R¹⁶, (14) ring 5, (15) -O-ring 5, (16) C1-10 alkyl substituted by ring 5, (17) C2-10 alkenyl substituted by ring 5, (18) C2-10 alkynyl substituted by ring 5, (19) C1-10 alkoxy substituted by ring 5, (20) C1-10 alkyl substituted by -O-ring 5, (21) -COOR¹⁷, (22) C1-10 alkoxy substituted by 1 to 4 halogen atom(s), (23) formyl, (24) C1-10 alkyl substituted by hydroxy or (25) C2-10 acyl,

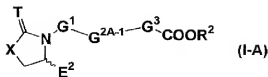
R¹⁵, R¹⁶ and R¹⁷ are each independently (1) hydrogen atom or (2) C1-10 alkyl, ring 5 may be substituted by 1 to 3 substituent(s) selected from the following (1) to (9); (1) C1-10 alkyl, (2) C2-10 alkenyl, (3) C2-10 alkynyl, (4) C1-10 alkoxy, (5) C1-10 alkyl substituted by C1-10 alkoxy, (6) halogen atom, (7) hydroxy, (8) C1-10 alkyl substituted by 1 to 3 halogen atom(s), (9) C1-10 alkyl substituted by C1-10 alkoxy substituted by 1 to 3 halogen atom(s);

ring 1, ring 2, ring 3, ring 4 and ring 5 are each independently (1) cyclic hydrocarbon or (2) heterocyclic ring,

----- is a single or double bond,

~~~~ is  $\alpha$ -configuration,  $\beta$ -configuration or a mixture thereof, a salt thereof, a solvate thereof or a cyclodextrin clathrate thereof.

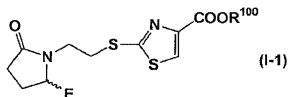
6. The pharmaceutical composition according to claim 5, wherein the compound represented by formula (I) is a compound represented by formula (I-A):



wherein  $G^{2A-1}$  is  $-Y^a$ -ring 1-,  $Y^a$  is  $-S-$ ,  $-SO_2-$ ,  $-O-$  or  $-NR^{1-}$ , the other symbols have the same meanings as described in claim 5.

8. The pharmaceutical composition according to claim 5, wherein  $R^2$  is C7-20 aliphatic hydrocarbon which may have a substituent(s).

8. The pharmaceutical composition according to claim 5, wherein the compound represented by formula (I) is a compound represented by formula (I-1):



wherein  $R^{100}$  is a hydrocarbon which may have a substituent(s), the other symbols have the same meanings as described in claim 5.

9. The pharmaceutical composition according to claim 8, wherein  $R^{100}$  is an aliphatic hydrocarbon having 3 to 22 carbon atoms in its main chain which may have a substituent(s).

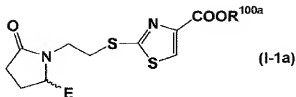
10. The pharmaceutical composition according to claim 5, wherein the compound represented by formula (I) is 2-[(2R)-2-[(2-chloro-4-heptylphenoxy)methyl]-5-oxo-1-pyrrolidinyl)ethyl]sulfanyl]-1,3-thiazole-4-carboxylic acid, undecyl 2-[(2-[(2R)-2-[(3,5-dichlorophenoxy)methyl]-5-oxo-1-pyrrolidinyl)ethyl]sulfanyl]-1,3-thiazole-4-carboxylate, 10-phenyldecyl 2-[(2-[(2R)-2-[(3,5-dichlorophenoxy)methyl]-5-oxo-1-pyrrolidinyl)ethyl]sulfanyl]-1,3-thiazole-4-carboxylate, 10-phenyldecyl 2-[(2-[(5R)-2-oxo-5-[(3-(trifluoromethoxy)phenoxy)methyl]-1-pyrrolidinyl)ethyl]sulfanyl]-1,3-thiazole-4-carboxylate, undecyl 2-[(2-[(2R)-2-[(heptylamino)methyl]-5-oxo-1-pyrrolidinyl)ethyl]sulfanyl]-1,3-thiazole-4-carboxylate, 10-phenyldecyl 2-[(2-[(2R)-2-[(heptylamino)methyl]-5-oxo-1-pyrrolidinyl)ethyl]sulfanyl]-1,3-thiazole-4-carboxylate or 10-phenyldecyl 2-[(2-[(2R)-2-[(1E)-1-nonenyl]-5-oxo-1-pyrrolidinyl)ethyl]sulfanyl]-1,3-thiazole-4-carboxylate.

12. The pharmaceutical composition according to claim 1, which is an agent for preventing and/or treating respiratory disease.

12. The pharmaceutical composition according to claim 11, wherein the respiratory disease is asthma, pulmonary injury, pulmonary fibrosis, pulmonary emphysema, bronchitis, chronic obstructive pulmonary disease, adult respiratory distress syndrome, cystic fibrosis or pulmonary hypertension.

13. A medicament which comprises a combination of the pharmaceutical composition for inhalation comprising the compound represented by formula (I) according to claim 5, a salt thereof, a solvate thereof or a cyclodextrin clathrate thereof, and one or more medicament(s) selected from type 4 phosphodiesterase inhibitor, steroids,  $\beta$ -agonist, leukotriene receptor antagonist, thromboxane synthetase inhibitor, thromboxane  $A_2$  receptor antagonist, mediator release inhibitor, anti-histamines, xanthine derivative, anticholinergic drugs, cytokine inhibitor, prostaglandins, forskolin preparation, elastase inhibitor, metalloprotease inhibitor, expectorant, antibiotics and immunosuppressive.

14. A compound represented by formula (I-1a):

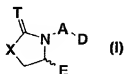


wherein  $R^{100a}$  is hydrocarbon which may have a substituent(s), with the proviso that (1) C1-10 alkyl, (2) phenyl, (3) C1-10 alkyl substituted by phenyl, (4) biphenyl, (5) C1-10 alkyl substituted by biphenyl which may be substituted by 1 to 3 substituent(s) selected from C1-10 alkyl, C1-10 alkoxy, or halogen, and (6) biphenyl which may be substituted by 1 to 3 substituent(s) selected from C1-10 alkyl, C1-10 alkoxy, or halogen are excluded, the other symbols have the same meanings as described in claim 5, a salt thereof, a solvate thereof or a cyclodextrin clathrate thereof.

15. The compound according to claim 14, wherein  $R^{100a}$  is C11-20 alkyl may have a substitutednt(s), C7-20 alkenyl may have a substitutednt(s) or C7-20 alkynyl may have a substitutednt(s), the salt thereof, the solvate thereof or the cyclodextrin clathrate thereof.

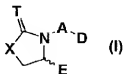
16. 2-[(2-[(2R)-2-[(2-chloro-4-heptyloxy)methyl]-5-oxo-1-pyrrolidinyl)ethyl)sulfanyl]-1,3-thiazole-4-carboxylic acid, undecyl 2-[(2-[(2R)-2-[(3,5-dichlorophenoxy)methyl]-5-oxo-1-pyrrolidinyl)ethyl)sulfanyl]-1,3-thiazole-4-carboxylate, 10-phenyldecyl 2-[(2-[(2R)-2-[(3,5-dichlorophenoxy)methyl]-5-oxo-1-pyrrolidinyl)ethyl)sulfanyl]-1,3-thiazole-4-carboxylate, 10-phenyldecyl 2-[(2-[(2R)-2-[(3-trifluoromethoxyphenoxy)methyl]-1-pyrrolidinyl)ethyl)sulfanyl]-1,3-thiazole-4-carboxylate, undecyl 2-[(2-[(2R)-2-[(heptylamino)methyl]-5-oxo-1-pyrrolidinyl)ethyl)sulfanyl]-1,3-thiazole-4-carboxylate, 10-phenyldecyl 2-[(2-[(2R)-2-[(heptylamino)methyl]-5-oxo-1-pyrrolidinyl)ethyl)sulfanyl]-1,3-thiazole-4-carboxylate or 10-phenyldecyl 2-[(2-[(2R)-2-[(1E)-1-nonenyl]-5-oxo-1-pyrrolidinyl)ethyl)sulfanyl]-1,3-thiazole-4-carboxylate, a salt thereof, a solvate thereof or a cyclodextrin clathrate thereof.

17. A method for preventing and/or treating respiratory disease which is characterized by inhalation administration effective dose of a compound represented by formula (I):



wherein all symbols have same meanings as described in claim 5, a salt thereof, a solvate thereof or a cyclodextrin clathrate thereof.

18. A use of a pharmaceutical composition for inhalation comprising a compound represented by formula (I):



wherein all symbols have same meanings as described in claim 5, a salt thereof, a solvate thereof or a cyclodextrin clathrate thereof for preparing an agent for preventing and/or treating respiratory disease.

FIG. 1

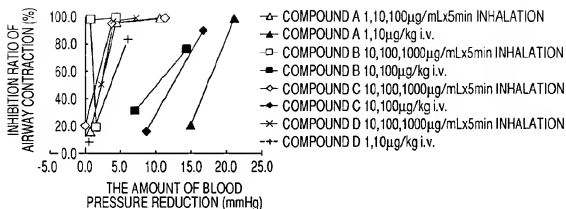


FIG. 2

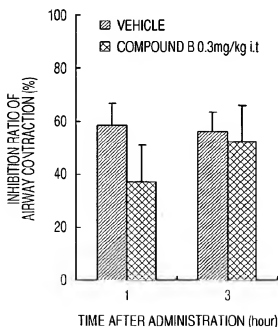


FIG. 3

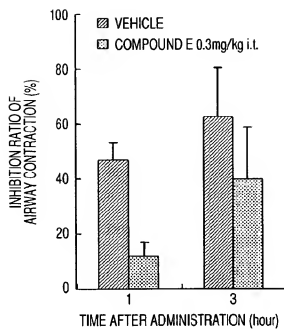


FIG. 4

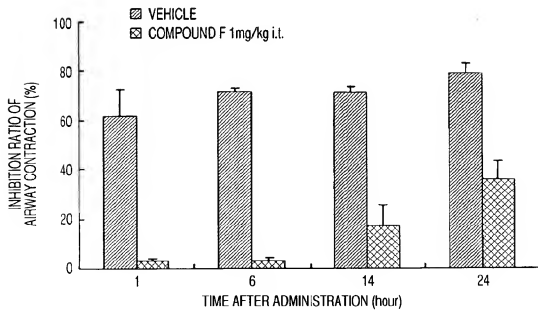


FIG. 5

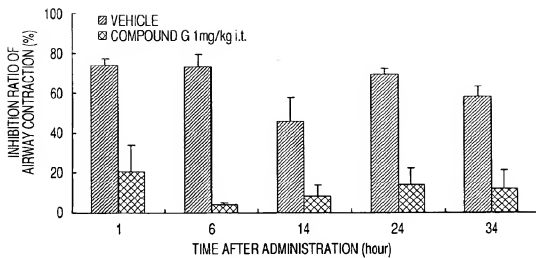


FIG. 6

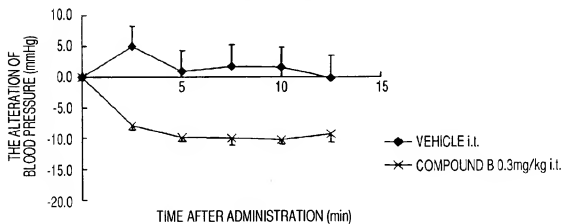


FIG. 7

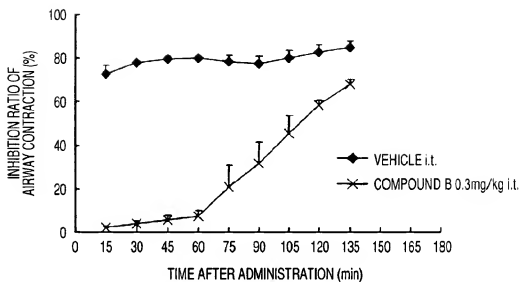


FIG. 8

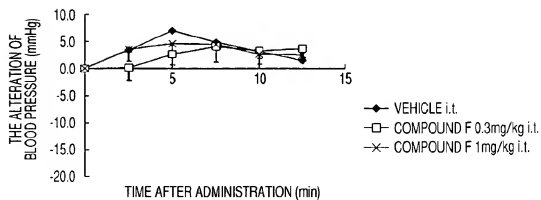
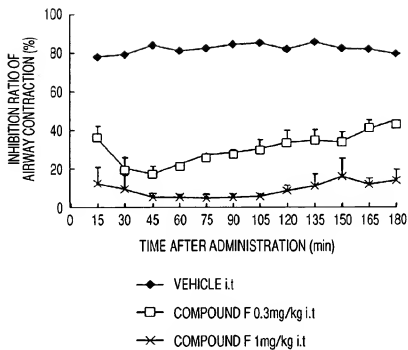


FIG. 9



## INTERNATIONAL SEARCH REPORT

International application No.  
PCT/JP2005/019376

| <b>A. CLASSIFICATION OF SUBJECT MATTER</b><br><b>A61K45/00</b> (2006.01), <b>A61K31/427</b> (2006.01), <b>A61P11/00</b> (2006.01), <b>A61P43/00</b><br>(2006.01), <b>C07D417/12</b> (2006.01)                                                                                                                                                                                                                                                                                                                                                                                                                          |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |                                                                                   |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------|
| According to International Patent Classification (IPC) or to both national classification and IPC                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |                                                                                   |
| <b>B. FIELDS SEARCHED</b><br>Minimum documentation searched (classification system followed by classification symbols)<br><b>A61K45/00</b> (2006.01), <b>A61K31/427</b> (2006.01), <b>A61P11/00</b> (2006.01), <b>A61P43/00</b><br>(2006.01), <b>C07D417/12</b> (2006.01)                                                                                                                                                                                                                                                                                                                                              |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |                                                                                   |
| Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched<br>Jitsuyo Shinan Koho 1922-1996 Jitsuyo Shinan Toroku Koho 1996-2006<br>Kokai Jitsuyo Shinan Koho 1971-2006 Toroku Jitsuyo Shinan Koho 1994-2006                                                                                                                                                                                                                                                                                                                                        |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |                                                                                   |
| Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)<br>CACLD (STN), CAPLUS (STN), REGISTRY (STN)                                                                                                                                                                                                                                                                                                                                                                                                                                              |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |                                                                                   |
| <b>C. DOCUMENTS CONSIDERED TO BE RELEVANT</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |                                                                                   |
| Category*                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              | Citation of document, with indication, where appropriate, of the relevant passages                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       | Relevant to claim No.                                                             |
| Y                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      | WO 2003/074483 A1 (ONO PHARMACEUTICAL CO., LTD.),                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        | 1-6, 8, 9,                                                                        |
| A                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      | 12 September, 2003 (12.09.03),<br>Full text<br>& JP 2003-572953 A & EP 1481976 A1<br>& US 2005/124577 A1                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 | 11-13, 16, 18<br>7, 10, 14, 15                                                    |
| Y                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      | JP 2004-517942 A (BOEHRINGER INGELHEIM PHARMA GMBH & CO KG, DE),<br>17 June, 2004 (17.06.04),<br>Par. No. [0001]<br>& WO 2002/60532 A1 & US 2002/189610 A1<br>& EP 1357975 A1                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            | 1-6, 8, 9,<br>11-13, 16, 18                                                       |
| <input checked="" type="checkbox"/> Further documents are listed in the continuation of Box C. <input type="checkbox"/> See patent family annex.                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |                                                                                   |
| * Special categories of cited documents:<br>'A' document defining the general state of the art which is not considered to be of particular relevance<br>'E' earlier application or patent but published on or after the international filing date<br>'L' document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)<br>'O' document referring to an oral disclosure, use, exhibition or other means<br>'P' document published prior to the international filing date but later than the priority date claimed | 'T' later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention<br>'X' document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone<br>'Y' document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art<br>'Z' document member of the same patent family |                                                                                   |
| Date of the actual completion of the international search<br>06 January, 2006 (06.01.06)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          | Date of mailing of the international search report<br>17 January, 2006 (17.01.06) |
| Name and mailing address of the ISA/<br>Japanese Patent Office                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          | Authorized officer                                                                |
| Examiner No.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          | Telephone No.                                                                     |

Form PCT/ISA/210 (second sheet) (April 2005)

## INTERNATIONAL SEARCH REPORT

International application No.

PCT/JP2005/019376

| C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT |                                                                                                                                                                                                                                                                                           |                                              |
|-------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------|
| Category*                                             | Citation of document, with indication, where appropriate, of the relevant passages                                                                                                                                                                                                        | Relevant to claim No.                        |
| Y                                                     | JP 09-501700 A (SCHERING CORP.),<br>18 February, 1997 (18.02.97),<br>Par. No. [0003]<br>& WO 95/20393 A1 & EP 740550 A1<br>& JP 11-286447 A & EP 1174138 A2<br>& EP 1174139 A2 & EP 740550 B1<br>& EP 1192945 A1 & EP 1201242 A2<br>& JP 2003-313128 A & JP 3480736 B2<br>& US 6723713 B2 | 1-6, 8, 9,<br>11-13, 16, 18                  |
| Y                                                     | JP 50-047967 A (SCHERING AG.),<br>28 April, 1975 (28.04.75),<br>Page 3, upper left column, line 4 to upper<br>right column, line 7<br>& US 4039668 A & JP 87045846 B                                                                                                                      | 1-6, 8, 9,<br>11-13, 16, 18                  |
| Y                                                     | Mitsuo MATSUMOTO, "Yakuzaijaku Manual", Nanzando,<br>1989, pages 30, 118, 119                                                                                                                                                                                                             | 1-6, 8, 9,<br>11-13, 16, 18                  |
| Y                                                     | Hitoshi SEZAKI, "Drug Delivery System", Nankodo<br>Co., Ltd., pages 49 to 57                                                                                                                                                                                                              | 1-6, 8, 9,<br>11-13, 16, 18                  |
| Y                                                     | Mitsuru HASHIDA, "Keiko Toyo Seizai no Sekkei<br>to HyoKa", Kabushiki Kaisha Yakugyo Jihosha,<br>1995, pages 216 to 231                                                                                                                                                                   | 1-6, 8, 9,<br>11-13, 16, 18                  |
| A                                                     | WO 2003/009872 A1 (CNO PHARMACEUTICAL CO.,<br>LTD.),<br>06 February, 2003 (06.02.03),<br>Full text<br>& EP 1417975 A1 & JP 2003-515264 A<br>& US 2005/020686 A1                                                                                                                           | 1-16, 18                                     |
| A                                                     | WO 2004/065365 A1 (CNO PHARM CO., LTD.),<br>05 August, 2004 (05.08.04),<br>Full text<br>& JP 2005-104836 A & EP 1586564 A1                                                                                                                                                                | 1-16, 18                                     |
| P,Y                                                   | WO 2005/061492 A1 (CNO PHARM CO., LTD., JP),<br>07 July, 2005 (07.07.05),<br>Full text<br>(Family: none)                                                                                                                                                                                  | 1-6, 8, 9,<br>11-13, 16, 18<br>7, 10, 14, 15 |
| P,A                                                   | WO 2005/053707 A1 (CNO PHARM CO., LTD., JP),<br>16 June, 2005 (16.06.05),<br>Full text<br>(Family: none)                                                                                                                                                                                  | 1-16, 18                                     |

Form PCT/ISA/210 (continuation of second sheet) (April 2005)

## INTERNATIONAL SEARCH REPORT

International application No.

PCT/JP2005/019376

**Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)**

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

- 1 ☒ Claims Nos.: 1/7  
because they relate to subject matter not required to be searched by this Authority, namely:  
Claim 17 pertains to methods for treatment of the human body by therapy and thus relates to a subject matter which this International Searching Authority is not required, under the provisions of Article 17(2)(a)(i) of the PCT and Rule 39.1(iv) of the Regulations under the PCT, to search.
- 2 ☐ Claims Nos.:  
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
- 3 ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

**Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)**

This International Searching Authority found multiple inventions in this international application, as follows:

- 1 ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
- 2 ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
- 3 ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
- 4 ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

**Remark on Protest**  
the

- ☐ The additional search fees were accompanied by the applicant's protest and, where applicable, payment of a protest fee.
- ☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
- ☐ No protest accompanied the payment of additional search fees.

Form PCT/ISA/210 (continuation of first sheet (2)) (April 2005)

## INTERNATIONAL SEARCH REPORT

International application No.

PCT/JP2005/019376

## &lt;Subject of search&gt;

Claims 1 to 4, 11 to 13 and 18 relate to medicinal compositions for inhalation which contain a compound defined by a desired property as "an EP2 agonist" as the active ingredient. Although claims 1 to 4, 11 to 13 and 18 involve any compounds having this property, it appears that only small part of the claimed compounds are supported by the description in the meaning within PCT Article 6 and disclosed therein in the meaning within PCT Article 5.

Even though the common technical knowledge at the point of the application is taken into consideration, the scopes of the compounds being "an EP2 agonist", "a continuous-release type prodrug"/"a prodrug having a relieved effect of lowering blood pressure"/"an ester of a long-chain aliphatic alcohol or an amide of a long-chain aliphatic amine", "a prodrug" and so on cannot be specified. Thus, claims 1 to 4, 11 to 13 and 18 do not comply with the requirement of clearness in accordance with PCT Article 6.

Moreover, the statements in claims 2 to 4 make it unclear to what extent of structures of compounds fall within the category of "prodrug". Namely, it is impossible in practice to search in detail and present all documents citing such compounds.

The active ingredient of the medicinal compositions according to claims 5 to 7 involve various compounds over an extremely large scope and complete search can be hardly made on all of these compounds. On the other hand, it appears that only small part of the active ingredients of the medicinal compositions according to claims 5 to 7 are supported by the description in the meaning within PCT Article 6 and disclosed therein in the meaning within PCT Article 5.

Such being the case, the inventions according to claims 1 to 7, 11 to 13 and 18 and the description do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out.

Such being the case, the international search was made on the compounds specifically cited in the description within a reasonable scope of burden. Complete search was made on claims 10 and 14 to 16.

# REFERENCES CITED IN THE DESCRIPTION

*This list of references cited by the applicant is for the reader's convenience only. It does not form part of the European patent document. Even though great care has been taken in compiling the references, errors or omissions cannot be excluded and the EPO disclaims all liability in this regard.*

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- WO 200374483 A [0005] [0102]
- EP 860430 A [0013] [0101]
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- WO 9933794 A [0013] [0101]
- EP 974580 A [0013] [0101]
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- JP 52031404 B [0100]
- JP 61052146 B [0100]

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- ELMER J. RAUCKMAN. *J. Org. Chem.*, 1976, vol. 41 (3), 564-565 [0111]
- KONZETT, H. ; ROESSLER, R. Versuchsanordnung zu untersuchungen ender Bronchial- muskulatur. *Arch Exp Pathol Pharmacol*, 1940, vol. 195, 71-74 [0180]